10mg versus 5mg initiation dose of Warfarin to achieve adequate anticoagulation in the treatment of acute deep vein thrombosis - A Randomized Control Trial

A dissertation submitted in partial fulfilment of M.S. General Surgery Branch I Examination of the Tamil Nadu Dr M.G.R. UNIVERSITY, CHENNAI to be held in 2016.

Certificate

This is to certify that the dissertation "10mg versus 5mg initiation dose of Warfarin to achieve adequate anticoagulation in the treatment of acute deep vein thrombosis - A Randomized Control Trial." is a Bonafide work of Dr Srujan Lam Sharma carried out under our guidance towards the M.S. Branch I (General Surgery) Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in 2016.

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Declaration Certificate

This is to certify that the dissertation titled "10mg versus 5mg initiation dose of Warfarin to achieve adequate anticoagulation in the treatment of acute deep vein thrombosis - A Randomized Control Trial" which is submitted by me in partial fulfilment towards M.S. Branch I (General Surgery) Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in 2016 comprises only my original work and due acknowledgement has been made in text to all material used.

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I would like to express my gratitude to my guide Dr. Sukria Nayak for his steadfast guidance and unwavering support in the conduct of this trial and preparation of this dissertation. I am equally indebted to Dr. Sunil Agarwal for his invaluable suggestions and the clarity he brought in times of doubt.

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I would also like to thank the Department of Vascular Surgery for their help in running this trial despite their busy schedules.

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Finally I would like to thank the patients for their effort and contribution without which this would not have come to fruition

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10mg versus 5mg initiation dose of Warfarin to achieve adequate anticoagulation in the treatment of acute deep vein thrombosis – A randomized control trial.
Dr. Srujan Sharma, General Surgery, Dr. Sukria Nayak, General Surgery,
Dr. Sunil Agarwal, Vascular Surgery, Dr. L. Jeyaseelan, Biostatistics,
Dr. Indrani Sen, Vascular Surgery.

Ref: IRB Min No: 8575 [INTERVEN] dated 27.11.2013

Dear Dr. Srujan Sharma,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
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Dr. Sunil Agarwal, Vascular Surgery, Dr. L. Jeyaseelan, Biostatistics,
Dr. Indrani Sen, Vascular Surgery.

Ref: IRB Min No: 8575 [INTERVEN] dated 27.11.2013

Dear Dr. Srujan Sharma,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "10mg versus 5mg initiation dose of Warfarin to achieve adequate anticoagulation in the treatment of acute deep vein thrombosis – A randomized control trial." on November 27th, 2013.

The Committee reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' Drs. Srujan Sharma, Sukria Nayak, Sunil Agarwal, L. Jeyaseelan, Indrani Sen.
3. Information & Consent form (English, Tamil, Hindi &Bengali)
4. No of documents 1-3

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on November 27th, 2013at 9.45 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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Dr. Molly Jacob	MBBS, MD, PhD	Professor, Biochemistry, CMCH.	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, CMCH.	Internal, Clinician
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Dr. Sukriya Nayak	MBBS, MS	Professor, General Surgery, CMCH	Internal, Clinician
Dr. Deepak Abraham	MBBS, MS	Professor, Endocrine Surgery, CMCH.	Internal, Clinician
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Dr. B. Antonisamy	M.Sc, PhD, FSMS, FRSS	Professor, Biostatistics, CMCH, Member Secretary, Research Committee, IRB.	Internal, Statistician
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Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
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Rev. Dr. T. Arul Dhas	M.Sc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMCH.	Internal, Social Scientist
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Mrs. Mary Johnson	M.Sc	Professor, Child Health Nursing	Internal, Nurse
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMCH.	Internal, Legal Expert
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Hence we approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent.** On completion of the study you are expected to submit a copy of the **final report.** Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 60,000 INR (Rupees Sixty Thousand only) will be granted for 18 months

The trial need to be registered with Clinical Trial Registry India (CTRI) http://ctri.nic.in before commencing.

The study will need to be submitted to a three monthly data-safety monitoring board (DSMB) review with duly filled in form found in the link http://172.16.11.136/Research/IRB_Polices.html

In case of adverse event, it has to be reported to the IRB Compensation Committee with duly filled in SAE format addressed to Dr. Denise Fleming, Clinical Pharmacology, CMC as a hard copy. The soft copy addressed to saeclinpharm@gmail.com and copy to research@cmcvellore.ac.in.

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Yours sincerely

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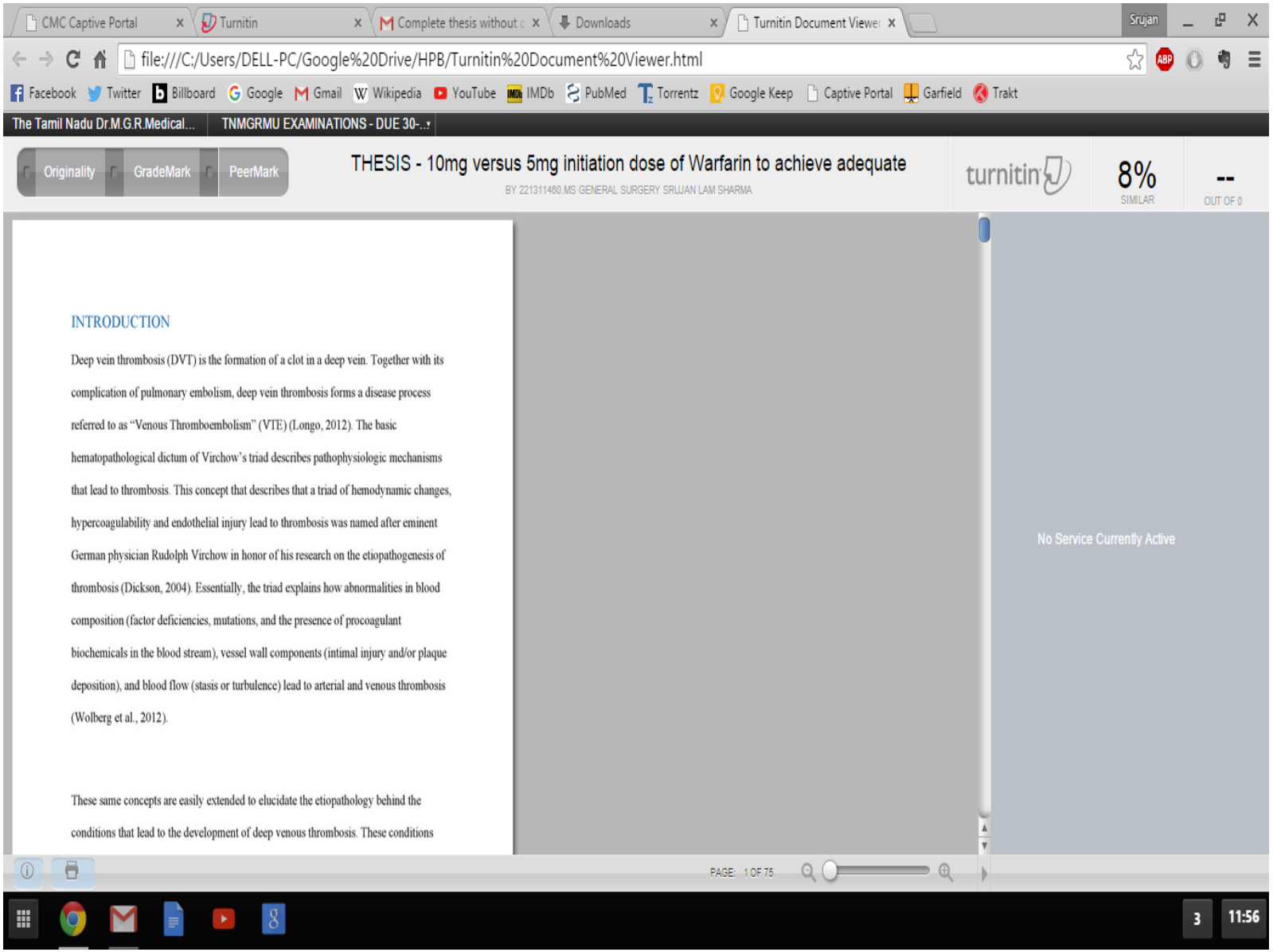
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INTRODUCTION
Deep vein thrombosis (DVT) is the formation of a clot in a deep vein. Together with its complication of pulmonary embolism, deep vein thrombosis forms a disease process referred to as "Venous Thromboembolism" (VTE) (Longo, 2012). The basic hematopathological dictum of Virchow's triad describes pathophysiologic mechanisms that lead to thrombosis. This concept that describes that a triad of hemodynamic changes, hypercoagulability and endothelial injury lead to thrombosis was named after eminent German physician Rudolph Virchow in honor of his research on the etiopathogenesis of thrombosis (Dickson, 2004). Essentially, the triad explains how abnormalities in blood composition (factor deficiencies, mutations, and the presence of procoagulant biochemicals in the blood stream), vessel wall components (intimal injury and/or plaque deposition), and blood flow (stasis or turbulence) lead to arterial and venous thrombosis (Wolberg et al., 2012).
These same concepts are easily extended to elucidate the etiopathology behind the conditions that lead to the development of deep venous thrombosis. These conditions
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INTRODUCTION

Deep vein thrombosis (DVT) is the formation of a clot in a deep vein. Together with its complication of pulmonary embolism, deep vein thrombosis forms a disease process referred to as "Venous Thromboembolism" (VTE) (Longo, 2012). The basic hematopathological dictum of Virchow's triad describes pathophysiologic mechanisms that lead to thrombosis. This concept that describes that a triad of hemodynamic changes, hypercoagulability and endothelial injury lead to thrombosis was named after eminent German physician Rudolph Virchow in honor of his research on the etiopathogenesis of thrombosis (Dickson, 2004). Essentially, the triad explains how abnormalities in blood composition (factor deficiencies, mutations, and the presence of procoagulant biochemicals in the blood stream), vessel wall components (intimal injury and/or plaque deposition), and blood flow (stasis or turbulence) lead to arterial and venous thrombosis (Wolberg et al., 2012).

These same concepts are easily extended to elucidate the etiopathology behind the conditions that lead to the development of deep venous thrombosis. These conditions may be idiopathic, inherited or acquired in origin and the resultant venous thrombosis maybe classified accordingly (Longo, 2012). Alternatively and more commonly, deep venous thrombosis is classified as provoked or unprovoked based on the presence or absence of a known pre-existing risk factor at the time of onset of disease. Logically, the etiopathogenesis of unprovoked deep venous thrombosis is either idiopathic or due to

inherited conditions such as Protein C or Protein S deficiency, while provoked deep venous thrombosis usually arises in the setting of an acquired thrombophilic state like malignancy, prolonged bed rest after major surgery, trauma or systemic lupus erythematosus (Townsend, 2012).

Since venous thromboembolism represents a significant disease burden (Anderson et al., 1991; Beckman et al., 2010; "Data and Statistics | DVT/PE | Centers for Disease Control and Prevention," 2015; Silverstein et al., 1998; Yeo et al., 2014), and especially considering the shift of disease and mortality from infectious causes to non-communicable diseases in the past century and ever increasing overall life expectancy rates (Raskob et al., 2014), venous thromboembolism is increasingly becoming an important focus of clinical and laboratory research.

In the clinical setting, acute deep venous thrombosis in an extremity usually presents with swelling and pain of the said extremity (N. C. G. C. Royal College of Physicians, 2012). While the pain and swelling themselves can cause significant debilitation in the short term, and deep venous thrombosis can also lead to the significant morbidity of post thrombotic syndrome (Kahn et al., 2008; Vazquez et al., 2009), the biggest impetus for the treatment of deep venous thrombosis remains the threat of pulmonary embolism and possibility of consequent mortality (Wells et al., 2014).

The Royal College of Physicians and the American College of Chest Physicians routinely publish and update guidelines on the prevention and management of VTE (ACCP, 2012; Royal College of Physicians, 2012). While there are some strong recommendations regarding some aspects of therapeutic anticoagulation, several currently recommended guidelines are still based on weak levels of evidence (Holbrook et al., 2012).

One such area of contention is the loading dose of the vitamin K antagonist and oral anticoagulant warfarin while initiating the recommended overlap with parenteral anticoagulation (Holbrook et al., 2012). The competing protocols essentially require two consecutive days of either 5mg or 10mg with further dose adjustments based on level of anticoagulation assessed by the Prothrombin Time blood test. Several small randomized controlled trials have already been conducted to try and determine which the better protocol is (Farahmand et al., 2011; Kovacs et al., 2003, 1999; Quiroz et al., 2006). However a recent Cochrane meta-analysis has determined that there was still considerable doubt regarding the benefits of either protocol over the other (Garcia et al., 2013).

In the light of the results of this meta-analysis, and the absence of published data regarding the same "loading dose" question from Asia and particularly the Indian

subcontinent, the investigators of this study chose to research this important topic. The following dissertation describes a randomized control trial that attempts to understand if the 10mg initiation dose achieves anticoagulation faster than the 5mg initiation dose in the treatment of acute deep vein thrombosis, while maintaining safety and efficacy.

AIMS AND OBJECTIVES

PRIMARY OBJECTIVES

1) To determine if a 10 mg initiation dose achieves adequate anticoagulation faster than 5 mg initiation dose.
2) If the 10mg initiation dose achieves adequate anticoagulation safely.

SECONDARY OBJECTIVES

1) To assess the clinical profile of patients presenting to our institution with deep venous thrombosis
2) To obtain basic demographic variables of age and sex
3) To assess which parenteral anticoagulant was used for the overlap period.

LITERATURE REVIEW

THE BURDEN OF DISEASE

The global burden of venous thromboembolism is difficult to estimate, with few population based studies done in this area. Most data comes from studies either extrapolating rates of DVT based on hospital data to rates in the population or studies on DVT in hospitalized patients who develop the disease while admitted. It has been estimated that venous thromboembolism is next only to acute coronary syndromes and stroke as a vascular cause of morbidity and mortality (National Institutes of Health. National Heart, Lung, and Blood Institute, 1998). The epidemiology of this disease process is mostly based on studies done more than two decades ago (Anderson et al., 1991; Silverstein et al., 1998). Both Anderson and Silverstein estimated the annual incidence of deep venous thrombosis in the population was 48 per 100000 individuals. The rates of pulmonary embolism in these two studies were significantly different with Anderson estimating an incidence of 23 per 100000 and Silverstein estimating 69 per 100000. Anderson also estimated a significantly high case fatality rate of 12% for inpatients with venous thromboembolism. Silverstein also calculated that males have a higher overall incidence of venous thromboembolism compared to females at 130 per 100000 versus 110 per 100000. The same study also noted a marked overall increase in the incidence of venous thromboembolism with age for both males and females. Anderson et al also noted the temporal profile of this disease process, documenting the clinical course of disease after discharge. They estimated that the long term case fatality

rates of this disease process at 1, 2 and 3 years after discharge from the initial hospital visit were 19%, 25%, and 30%. Anderson et al also estimated that 170000 new cases and 99000 recurrent cases of venous thromboembolism were treated at hospitals in the United States every year. While there have been significant improvements in the detection, treatment and prevention of venous thromboembolism since these studies were conducted, new epidemiological studies are hard to find. Spencer et al in 2006 published data concerning incidence rates of DVT for the year 1999 in the same geographic area Anderson et all studied a decade previously in the mid to late 1980s. They estimated an annual incidence of 104 per 100000 for venous thromboembolism (Spencer et al., 2006), only slightly lower than the overall incidence of 117 per 100000 published by Anderson in 1991.

It is also important to note that there is a significant difference among rates of deep venous thrombosis among individuals of different racial origins. In a review published in 2005, Heit looked at rates of venous thromboembolism among various racial groups in the United States (Heit, 2005) and stated that the incidence of this disease among Caucasian Americans was around 117 per 100000. This rate is exactly the same as the number Silverstein estimated. Heit also concluded in the review that the incidence of venous thromboembolism among African Americans or Blacks was higher than the Whites, and that the incidence among Asian Americans, Pacific Islanders and Native Americans was lower.

The racial differences in rates of venous thromboembolism can most likely be attributed to the genetics of this disease process. Studies have shown that venous thrombosis is inherited in a complex manner further complicated by environmental interactions (Heit et al., 2004; Larsen et al., 2003; Souto et al., 2000). Based on the results of a twin based study in Denmark, it has also been noted that genetic factors play more of a role in males than females (Larsen et al., 2003).

Survival after venous thromboembolism remains an issue of concern, with risk of mortality after pulmonary embolism 18 times higher than for deep venous thrombosis alone (Heit et al., 1999). This finding further highlights the very real need to prevent, diagnose and manage deep venous thrombosis appropriately. It has also been noted that pulmonary embolism, on its own, is an independent predictor of worse outcome in the form of reduced survival for up to three months after onset of disease (Heit, 2005).

Another concern is the significant morbidity of recurrent VTE. It has been estimated that up to 30% of all patients with DVT will have a recurrent episode in 10 years, with the risk of recurrence highest in the first six months following the initial attack (Heit, 2012). It has also been noted that while active anticoagulation during the initial period of treatment itself prevents recurrence there is no decreased risk of recurrence with increased duration of anticoagulation (Agnelli et al., 2003, 2001; Kearon et al., 1999; Pinede et al., 2001; Schulman et al., 1997; van Dongen CJ et al., 2003). This has been

extrapolated to mean that a certain subset of individuals is likely to go on to require lifelong secondary anticoagulation (Heit, 2005), and various risk factors have been studied to try and determine what exactly predisposes an individual to recurrent attacks of venous thromboembolism (Heit, 2012).

Most recently, and alarmingly it has been noted that occurrence of venous thromboembolism is fairly constant, if not on an upward trend (Heit, 2015). This is despite improved preventive and diagnostic abilities and the availability of effective therapy and prophylaxis. Studies have also noted that while venous thromboembolism generally affects males more frequently than females, pregnancy, puerperium and usage of oral contraceptive pills increase the risk of disease in women of childbearing age (Heit, 2015; Spencer et al., 2006).

The incidence of this disease process in Asian nations has traditionally been considered to be low, even in the context of pre-existing high risk factors (Sharma et al., 2009; Yeo et al., 2014). Yeo et al reviewed 14 publications gathering data from 11,218 Asian patients. They calculated that among the observational studies, the median incidence of proximal deep venous thrombosis was 0.08 % with a range of 0–2.9 %, while the median incidence of pulmonary embolism was 0.18 % with a range of 0–0.58 %. The rates of deep venous thrombosis in the control groups of the studies were up to 7.4 %, while the incidence of pulmonary embolism was up to 1.9 %.

Sharma et al, from the All India Institute of Medical Sciences, New Delhi, studied hospitalized patients with medical illnesses with reduced mobility and other risk factors for deep venous thrombosis. They found that the incidence of deep venous thrombosis per 1000 person days of hospital stay was only 2.7 (Sharma et al., 2009). Their findings indicated that the overall incidence of deep venous thrombosis in these patients, while higher than the non-hospitalized population, remained much lower than the rates noted in the available western data. Another study from the South of India, attempted to understand the prevalence of the known risk factor of hyperhomocysteinemia in patients with deep venous thrombosis (Kamat et al., 2010). They found that in patients with deep venous thrombosis admitted at their center, the prevalence of hyperhomocysteinemia was 31.428%, with more males affected than females.

In the two Indian studies noted, while the Sharma et al findings indicated a low rate of deep venous thrombosis in the population (by extrapolating from the low rate of deep venous thrombosis that patients had while admitted at the hospital), Kamat et al found a significantly high risk of hyperhomocysteinemia. It remains to be conclusively understood if deep venous thrombosis tends to occur mostly in the genetically susceptible members of the Indian population. There is also a significant concern of gross under-reporting of venous thromboembolism as a whole. This is a problem arising from the fact that there is significant difficulty of access to even primary healthcare for large portions of our population, let alone the ability to gain access to a center that could accurately

diagnose and appropriately treat venous thromboembolism. Added to this is the problem of the low rates of autopsy in India (Moorchung et al., 2013), which might mean that several deaths due to venous thromboembolism are not detected and therefore not documented. Therefore the epidemiology of this disease process in India remains largely unknown.

MANAGEMENT OF DEEP VENOUS THROMBOSIS

Understandably, the occurrence of deep venous thrombosis leads to the distal congestion of venous flow. As stated earlier, when occurring in an extremity it presents with swelling and pain of the said extremity (Royal College of Physicians, 2012). This swelling and pain may or may not be associated with symptoms of pulmonary embolism that may range from asymptomatic, to mild chest pain and breathlessness to something far more dramatic and critical such as sudden cardiovascular collapse and arrest.

The diagnosis of acute deep venous thrombosis is usually carried out with the combination of clinical suspicion, laboratory testing of fibrin degradation products (D-Dimer) and clinical ultrasound examination with Doppler flow assessment and venous compression studies. Of these the ultrasonological examination remains the diagnostic standard with negative predictive values of 97 to 98% (Bates et al., 2012; Michiels et al., 2015). Several protocols and scoring systems have been devised to help determine what test to use when suspecting deep venous thrombosis in a patient, chiefly because

ultrasound examination is time consuming and expensive (ACCP, 2012; Longo, 2012; Michiels et al., 2015; N. C. G. C. Royal College of Physicians, 2012).

The most commonly used clinical predictor of deep venous thrombosis is the Wells' scoring system (Wells et al., 1997). The scoring system states that a low score is 0, a moderate score 1 to 2, and a high score is 3 or more. The parameters used and scores are listed in the table below.

The usage of D-dimer assay as a predictor of deep venous thrombosis must be considered in the light of the Wells score. It is more useful as a negative predictor of deep venous thrombosis in patients with low Wells' scores and can be used to safely exclude these patients from the burden and expense of an additional ultrasonological examination (Wells et al., 2003). Therefore, the combination of Wells' scoring and D-dimer assay can be effectively and safely used in excluding deep venous thrombosis and therefore reduce the load of compression ultrasound examinations otherwise required.

The Wells' score for prediction of deep venous thrombosis (Wells et al., 1997) :

Parameter	Score
Active cancer (with treatment ongoing, within previous 6 months or palliative)	1
Paralysis, paresis or recent plaster immobilization of lower extremities	1
Recently bedridden for more than 3 days or major surgery within 4 weeks prior to onset of symptoms	1
Localized tenderness along the distribution of the deep vein system	1
Swelling of the entire leg	1
Calf swelling by more than 3 cm when compared with the other, if asymptomatic, leg	1
Pitting oedema of the leg in concern	1
Collateral superficial veins on the suspected side	1
Alternative diagnosis being as likely or greater than that of DVT	–2
DVT = deep vein thrombosis.	

However in most patients with moderate scores and all patients with high scores a radiological examination is usually required to confirm the diagnosis ("Deep Vein

Thrombosis (DVT) Diagnosis - Signs & Symptoms," 2015). The radiological test most commonly used is compression ultrasound (Turpie et al., 2002). Alternatively computed tomography venography or magnetic resonance imaging may be used. Despite some drawbacks such as lack of sensitivity in patients with oedema or significant obesity, operator dependence and inability to distinguish between an old thrombus and a fresh thrombus, compression ultrasonography is considered acceptable when combined with a probability score based on clinical variables such as the Wells' score ("Deep Vein Thrombosis (DVT) Diagnosis - Signs & Symptoms," 2015).

However the historical gold standard for confirmation of deep venous thrombosis remains the invasive modality of conventional venography (Wheeler and Anderson, 1995). However, ultrasound had taken over as the diagnostic standard as early as two decades ago (Wheeler and Anderson, 1995). With the non-invasive nature of ultrasonology, the increasing ease of access and lack of concerns regarding invasiveness and contrast related complications it is easy to understand why most clinical practice shifted to this modality. Another modality that has been described as early as 1979, albeit rarely used is thermography (Ritchie et al., 1979). Thermal imaging is still being studied as an addition to the armamentarium of diagnostic modalities available in the diagnosis of deep venous thrombosis (Deng et al., 2015). Several new modalities are also being researched in the diagnosis of deep vein thrombosis, including thrombin generation and

proteomics, thrombus-targeted molecular imaging, and infrared thermal imaging (Lippi et al., 2015).

Once the diagnosis of acute deep venous thrombosis is established, it is of paramount importance to initiate appropriate therapeutic measures, so as to prevent the significant morbidity of this disease process as described earlier. The objectives of therapy of deep venous thrombosis and pulmonary embolism (Hirsh and Hoak, 1996) are summarized below:

1) Prevention of local extension of the thrombus
2) Prevention of embolization of the thrombus
3) To accelerate fibrinolysis, albeit, only in certain clinical circumstances

Anticoagulants have been found to be effective in achieving these very objectives as early as 1960 (Barritt and Jordan, 1960). This especially true when it comes to preventing clinically important extension of thrombus (Hirsh and Hoak, 1996). Just like with the diagnosis of deep venous thrombosis, several treatment protocols exist concerning themselves with just how exactly to use these anticoagulants when it comes to the treatment of this disease. The current conventions involve initiation of an injectable/parenteral anticoagulant (usually unfractionated or low molecular weight heparin) while overlapping with an oral vitamin k antagonist (most commonly, warfarin)

(Weinmann and Salzman, 1994). The reason for this is the fact that vitamin K antagonists need time to start effectively acting against the prothrombotic mechanisms in place. This is because the antithrombotic effect of warfarin requires reduction of factor II (also known as prothrombin), which has a significantly long half-life of sixty to seventy two hours, as compared to the six to twenty four hours for the factors such as factor VII, factor IX and factor X, that are responsible for the more rapid anticoagulant effect of the drug (Hirsh et al., 2003). Heparin meanwhile has a relatively faster effect, being a sulfated glycosaminoglycan that enacts its anticoagulant effect essentially by binding to antithrombin (Hirsh et al., 2001; McRae and Ginsberg, 2004). It then induces conformational changes that greatly increase the rate at which antithrombin inhibits coagulation enzymes, therefore effectively providing an adequate antithrombotic effect (Hirsh et al., 2001; McRae and Ginsberg, 2004).

It is important to note that the level of parenteral anticoagulation achieved initially must be adequate. It has been shown that suboptimal initial anticoagulation was associated with significantly higher recurrence rates and therefore it is of utmost importance to dose the patient adequately (Hull et al., 1986).

A easy to understand approach for the treatment of deep venous thrombosis divides treatment into three phases – acute, long term and extended (Becattini et al., 2012). The parenteral anticoagulants currently used for rapid anticoagulation in the acute phase are

unfractionated heparin, low molecular weight heparin and the synthetic pentasaccharide factor Xa inhibitor fondaparinux (Vo et al., 2014). For the long term and extended phases, oral anticoagulants, such as warfarin, remain the mainstay of therapy (Vo et al., 2014).

Therapy with warfarin however poses significant challenges. These include a slow initiation and slow reversal of anticoagulation, a narrow therapeutic window as described below, varied and unpredictable pharmacokinetics with the additional problems of significant food and drug interactions (Hirsh et al., 2003). There is also the necessary requirement for routine and regular monitoring and dose-adjustments to maintain anticoagulation within therapeutic range (Vo et al., 2014). Newer oral anticoagulants or NOACs have been developed that counter many of these challenges and several trials have been conducted to test their efficacy and safety (Kearon et al., 2012; Poulsen et al., 2012; Schulman and Crowther, 2012).

Warfarin however, with the decades of experience and data concerning its use, its easy availability and low cost remains the gold standard of therapy in our country and elsewhere (Kearon et al., 2012). Two trials conducted in the more than three decades ago established the need for long term oral anticoagulation with warfarin (Hull et al., 1979; Lagerstedt et al., 1985). Hull et al tackled the question of using long term low dose heparin versus oral anticoagulation with warfarin in the long term phase of treatment.

Hull et al recruited sixty-eight patients with acute deep vein thrombosis that was confirmed by conventional venography. These patients were treated with intravenous heparin in the acute phase of treatment and then randomized to secondary prophylaxis with low dose subcutaneous heparin or oral anticoagulation with warfarin. Nine of 35 patients receiving subcutaneous heparin developed new episodes of venous thromboembolism that were objectively documented. However no patient in the warfarin arm had a recurrence of venous thromboembolism or symptoms suggesting extension of the thrombus. There was a significant difference in the two arms of the trial with a P value of <0.001. However they also noted that seven patients in the warfarin arm had bleeding complications, four of which were major. Meanwhile no patient in the subcutaneous heparin arm had bleeding. This was also a significant finding with a P value <0.005. They thus concluded that warfarin successfullt prevented the complications of venous thromboembolism, albeit with a higher risk of bleeding.

Lagerstedt et al tackled the question of whether or not long term anticoagulation with warfarin was required in patients with symptomatic calf vein thrombosis. No patient in the warfarin arm had a recurrence of disease. However they noted that eight patients in the non-warfarin group out of twenty-eight developed a recurrence within the first three months. Out of those eight, five had proximal extension of the thrombus and one even had pulmonary embolism. Nineteen of these twenty eight patients went on to develop

recurrence of symptoms within the year. Only one patient on the warfarin arm had a recurrence at one year. The differences in the two arms were clearly significant.

It is likely that the high rate of bleeding that Hull et al noted was due to over-anticoagulation. They subsequently published in 1982 that dose adjusted heparin was safer and probably as effective as warfarin in long term anticoagulation, upon completion of their randomized trial (Hull et al., 1982). Subsequent studies have gone on to establish that the safe therapeutic range of therapy for warfarin is a Prothrombin Time International Normalized Ratio (PT(INR)) value of 2 to 3 (Fitzmaurice et al., 2002; Levine et al., 1992). These have shown that a higher range of therapy with targets of 3 to 4.5 are associated with significantly higher rates of bleeding without significantly better clinically relevant therapeutic levels (Caprini et al., 1999; Fitzmaurice et al., 2002; Levine et al., 1992).

The duration of therapy with oral anticoagulation is determined by a variety of factors. Most importantly, a distinction is made between provoked causes of deep venous thrombosis where the provoking factor no longer exists and unprovoked cases or cases such as active malignancy where the provoking factor continues to play a role (Kearon and Akl, 2014; Prandoni et al., 2011; Schulman et al., 1997, 1985). It is also important to note that the risk of recurrent VTE must be balanced with the risk of a major life threatening bleed. The presence of pulmonary embolism at initial presentation also

presents an additional factor determining duration of therapy and in certain cases, the need for intervention in the form of IVC filter placement (ACCP, 2012).

While pharmacological treatment remains the mainstay of therapy in the acute and long term phases of treatment of deep venous thrombosis and is the main area of concern of this trial, at this point it is also important to note the adjunct treatments practiced. While venous thrombectomy is not recommended in the treatment of deep venous thrombosis (ACCP, 2012), the role of thrombolysis is unclear. Thrombolytic therapy is better than heparin in producing causing fibrinolysis of the thrombus. However, significant disadvantages remain in the higher cost and higher bleeding risk (Goldhaber et al., 1984; Lensing and Hirsh, 1993). Consequently it is not routinely recommended in most patients with venous thromboembolism (ACCP, 2012). Thrombolysis however, does play a role in non-bleeding patients with hypotension after pulmonary embolism and maybe lifesaving (ACCP, 2012; Hirsh and Hoak, 1996). There is also limited evidence to suggest that thrombolysis reduces the rates of post thrombotic syndrome in certain patients with acute deep venous thrombosis (Elliot et al., 1979; Goldhaber et al., 1984).

Other Adjunct modalities used include caval interruption and inferior vena cava filter placement for patients with high risk of pulmonary embolism who have significant risk of bleeding if started on anticoagulation (Hirsh and Hoak, 1996). Further additional therapy may include compression stockings, compression therapy devices and other measures to

reduce local edema, although evidence for their efficacy remains unclear (ACCP, 2012; Fink, 2005; Hirsh and Hoak, 1996).

DEFINITION OF THE PROBLEM

The problem we tried to address in this study, as stated earlier, arises from the significant discrepancies in initiation protocols for warfarin in the acute phase of deep venous thrombosis treatment. The historical standard of treatment has been hospitalization, followed by initiation with 5mg of warfarin daily for two to three days, and then dose adjustment based on INR values (Garcia et al., 2013; Hirsh and Hoak, 1996; Lagerstedt et al., 1985; Longo, 2012; N. C. G. C. Royal College of Physicians, 2012; Turpie et al., 2002; Weinmann and Salzman, 1994; Wells et al., 2014). However, with advances in outpatient capabilities in the western world, the increased costs of treatment of this disease process (Spyropoulos and Lin, 2007), and the need for rapid and effective anticoagulation to prevent complications and recurrence (Hull et al., 1986) there has been an ever increasing push towards faster and more effective therapeutic regimens. Consequently, even the latest American College of Chest Physician guidelines recommend outpatient initiation of warfarin 10mg, albeit with the visors that the patient should be healthy enough for this higher level of therapy and outpatient care. It is important however to note that the grade of recommendation is a low 2C (Holbrook et al., 2012). This signifies the low levels of evidence this recommendation was based on and the need for further systematic and analytical studies in this area.

There have been several attempts to obtain some amount of clarity and to elucidate this significant area of concern. At least two Cochrane systematic reviews have been published since 2012 analyzing data from several randomized controlled trials comparing 5mg and 10mg initiation protocols (Garcia et al., 2013; Mahtani et al., 2012). While Mahtani et al compared all trials regardless of indication for initiation of therapy and Garcia et al specifically looked at trials comparing the two protocols in the treatment of deep venous thrombosis, both had similar conclusions. Both studies concluded that there was still a significant lack of evidence promoting the superiority of one protocol over the other. Additionally, Mahtani et al state that there was some evidence to suggest that lower doses were probably better in the elderly to offset the increased chance of bleeding. They also state that there was no evidence to support the pharmacogenetic testing of subjects to determine what dose of warfarin would be appropriate. This question arises from the fact that certain individuals with mutations in enzymes and receptors to warfarin clear the drug better or have high resistance to warfarin induced anticoagulation (Hirsh et al., 2003; Souto et al., 2000).

The impetus to this trial and the statistical calculation of sample sizes for this trial were from the four trials studied by Garcia et al (Farahmand et al., 2011; Kovacs et al., 2003, 1999; Quiroz et al., 2006) :

1) Kovacs et al, 1998
2) Kovacs et al, 2003
3) Quiroz et al, 2006

4) Farahmand et al, 2011

While the first three trials were based in the first world, the fourth, by Farahmand et al was based in Iran, a nation geographically and racially closer to our own country and population. All trials followed the standard dosing practice of an initiation loading dose followed by dose adjustment till two consecutive daily INR values within therapeutic target range of INR between 2 and 3, to allow assessment of stability of anticoagulation.

The first Kovac trial compared the effectiveness of a predetermined warfarin dose nomogram as compared to physician based administration in the treatment of primary (new onset) and secondary (recurrent) deep venous thrombosis. They concluded that using the devised nomogram was safe and led to a significantly shorter length of hospital stay in the patients studied. The second Kovac trial was a randomized, double blind, controlled trial that specifically studied the benefits of a 10mg dosing nomogram as compared to a 5mg dosing nomogram in 210 patients in a large Canadian City. They concluded that the 10mg nomogram achieved anticoagulation faster and recommended the same. Only one patient in each arm had a major bleeding complication in both arms. Quiroz et al conducted a randomized, open label, controlled trial recruiting 50 patients at a hospital in an American metropolitan city comparing a 10mg nomogram and a 5mg nomogram. This trial however found no statistical difference in the overall time to therapeutic target INR in both groups. There was one incident of major bleeding in the

10mg arm with an abdominal hematoma on day 4 of therapy with an INR of 2.2 (far below a level to be considered as the result of over-anticoagulation). They concluded that therefore there was no difference in using one dosage over the other. Farahmand et al conducted an emergency department based study of outpatients with deep venous thrombosis in Iran. Their study was randomized, double blind controlled trial and they also compared predesigned 10mg and 5mg nomograms. Similar to the second Kovacs trial this study also recommended 10mg initiation doses as they achieved faster anticoagulation. There was also no statistically significant or high rate of bleeding complications noted.

It is also important to note the revelations of a recent retrospective cross sectional audit study from our neighboring country Pakistan, which concluded that rate of anticoagulation with a 10mg nomogram was faster, albeit with the concern of an increased rate of over-anticoagulation (Chandriah et al., 2015).

Summarizing this review, it is clear that there are significant areas of concern regarding the lack of consensus for treatment of this disease process. The significant consequences of mismanaging venous thromboembolism present an urgent need for appropriate therapeutic guidelines. However, the large genetic and racial variations of the disease of venous thromboembolism itself, coupled with the significant differences of response to warfarin and its various in-vivo interactions present a mammoth task to both clinicians and research scientists alike.

JUSTIFICATION OF THE TRIAL

It is clear from the review of literature presented above that there is a real need for more answers when it comes to the question of appropriate therapy for deep venous thrombosis and by extension, venous thromboembolism. With the available published information there remains a considerable lack of certainty in the treatment of this significant cause of mortality and morbidity. Studies on DVT from India are rare and there has been no randomized trial published thus far in this area.

In light of these findings, the investigators of this trial decided to devise a randomized controlled trial at our center, a large South Indian tertiary referral hospital, studying if the 10mg initiation dose achieves anticoagulation faster than the 5mg initiation dose in the treatment of acute deep vein thrombosis, while maintaining safety and efficacy.

STUDY HYPOTHESIS:

"The 10mg initiation dose of warfarin achieves adequate anticoagulation faster than 5mg initiation dose in the treatment of acute deep venous thrombosis."

MATERIALS AND METHODS

This trial was approved by the Institutional Review Board and Ethics Committee of Christian Medical College, Vellore.

A randomized, open label, controlled trial was carried out. The 5mg initiation dose was compared with the 10mg initiation dose. After fulfilling the criteria listed below, 60 recruited patients were randomized before initiation of warfarin therapy to the 10mg or 5mg arm. The patients were started on parenteral anticoagulation with unfractionated heparin, low molecular weight heparin or fondaparinux. Initiation doses were administered for two days according to the trial arm and the INR was tested on the morning of the third day. Subsequent dosing was decided by the treating clinicians based on the responses of the tested INR value. In keeping with standard practice, warfarin dose initiation was overlapped with injectable anticoagulants, and INR testing was repeated daily until target INR was reached.

One of three options for parenteral anticoagulation was used – unfractionated heparin, low molecular weight heparin (enoxaparin or dalteparin), and fondaparinux. The dose of the injectable anticoagulants used in the acute phase of therapy were as follows:

1) Unfractionated Heparin: Initial intravenous bolus of 5000 units followed by a intravenous infusion at 18 units/kg adjusted to maintain an APTT value between 70 to 90 seconds.
2) Low Molecular Weight Heparins: 1mg/kg twice daily for enoxaparin or 100IU/kg twice daily for dalteparin.

3) Fondaparinux: 7.5mg once daily for body weight between 50 to 100kgs.

KEY CRITERIA

Inclusion Criteria:

1) Age of 18 or older
2) Diagnosed with acute deep venous thrombosis
3) Being started on oral anticoagulation therapy
4) Being treated by the Division of Surgery at our center.
5) Consenting to participation in the trial

Exclusion Criteria:

1) Weight less than 40 kilograms
2) Underlying liver or renal disease
3) Recent treatment with any anticoagulants (within the preceding 5 days)
4) Baseline INR >1.4
5) Pre-existing bleeding diatheses.
6) Diagnosed pulmonary embolism
7) Special patients (pregnancy, children)
8) Patients not consenting to participation in the trial

TRIAL METHODS

Method of randomization:

Block Randomization was carried out. That is, blocks of 2 and 4 for 40% and 60% respectively were made. These blocks were mixed and presented.

Method of allocation concealment:

Opaque sealed envelopes matching Patient Identification Number (with intervention arm concealed within) were prepared by the department of biostatistics and handed over to the Unit secretary to and kept under lock and key till the end of trial. On enrollment of a participant, the participant was assigned a serial Patient Identification Number. At this point the principal investigator procured the envelope bearing the specific Patient Identification Number and opened it to reveal the arm of trial the patient is being assigned to.

Blinding and masking:

The randomization process was blinded. Once the patient received a Patient Identification Number, the envelope bearing the number was handed to the principal investigator and the seal was broken to reveal which arm the patient was assigned to. No further blinding was done. The initiation doses were administered according to the randomization arm.

Subsequent management was based on the treating clinician's assessments. The patients could not be blinded as they needed to know the dose of the drug they were on to procure the same. The principal investigator who was administering consent to the patients needed to inform the patient of this dose and hence they too could not be blinded.

Consent Administration:

The principal investigator or the senior registrar in the unit took consent from the patient.

Primary Outcome:

The primary outcome was defined as the time to therapeutic INR. The stability of the INR was confirmed by two consecutive readings of between 2 to 3 at least 24 hours apart and recorded as time to stable INR and considered as the end of the trial.

Secondary Outcomes and End Points:

1) Death
2) Bleeding or over-anticoagulation(INR>8.0)
3) Failure to anticoagulate (Failure to achieve adequate anticoagulation despite maximum possible trial dose of 15mg of warfarin per day for three consecutive days)

STATISTICAL METHODS

Target sample size and rationale behind calculation:

The target sample size was calculated using data from the second randomized controlled trial by Kovac et al conducted in 2003 (Kovacs et al., 2003), and time to therapeutic INR was used as the primary end point. The 10mg arm in the said trial achieved primary end point 1.4 days earlier than 5mg arm. That is, the 10mg group achieved time to therapeutic INR by day 4.2(SD 1.1) days and 5mg group achieved time to therapeutic INR by day 5.6(SD 1.4). Using the Superiority method and the hypothesis that the 10mg dose achieves anticoagulation faster than the 5mg dose, as stated above, the following table was generated:

Standard deviation in group I	1.4
Standard deviation in group II	1.4
Mean difference	1.4
Effect size	1
Alpha error (%)	5
Power (1- beta) %	95
1 or 2 sided	2
Required sample size per group	26

The calculation of sample size was based on the formula:

$n = f(\alpha/2, \beta) \times 2 \times \sigma 2 / (\mu 1 - \mu 2)2$

In the above equation, $\mu 1$ and $\mu 2$ were the mean outcome in the control and experimental group respectively, σ was the standard deviation, and

$f(\alpha, \beta) = [\Phi\text{-}1(\alpha) + \Phi\text{-}1(\beta)]2$

(Φ-1 was the cumulative distribution function of a standardized normal deviate).

Therefore sample size calculated was N = 26 in each arm. The total requirement being 52, an additional 8 patients were added to the pretrial target recruitment value to account for lost data and attrition. Therefore the target sample size achieved was 60.

Methods for additional analyses:

The primary outcome was time to therapeutic INR which is a duration. We expected that every patient would have these INR values and since this duration did not deal with censoring, therefore it did not deal with survival concept. Data was be entered in EPIDATA software and was analyzed using the SPSS software. Data screening was done using Box-Cox plot, frequency distributions and histogram of the outcome variable. Q-Q plot and Shapiro Wilk test were done to test for normality. If normality assumption failed then we were prepared to use the non-parametric Mann- Whitney U test to compare the two groups. Since the data was normal, then difference between the two means and the 95% confidence interval was calculated. The conclusion was based on the 95% confidence interval. If there was an imbalance in the baseline variables, which was based on clinical judgment (not statistical) and then those variable effects were planned to be controlled using multivariable regression methods, however this was not necessary. As the outcome was measured during hospital stay, we thought it would be unlikely that we would have to deal with drop out or missing information. However, since there were drop outs the analyses will be based on both ITT and PP methods. Power analyses was not required as there was a significant difference in the primary outcome in between the two arms as noted below in the results section.

DETAILED ALGORITHM OF THE STUDY

Enrollment:

All patients with acute deep venous thrombosis, being initiated on oral anticoagulation with warfarin by the Division of Surgery were approached for recruitment, provided they met the key criteria as noted above.

Allocation:

Once consent was administered the patients were randomized to one of two arms, the first initiating them with a two day, once daily loading dose of 5mg warfarin and the second arm where they were administered 10mg once daily for two days as the inititiation protocol.

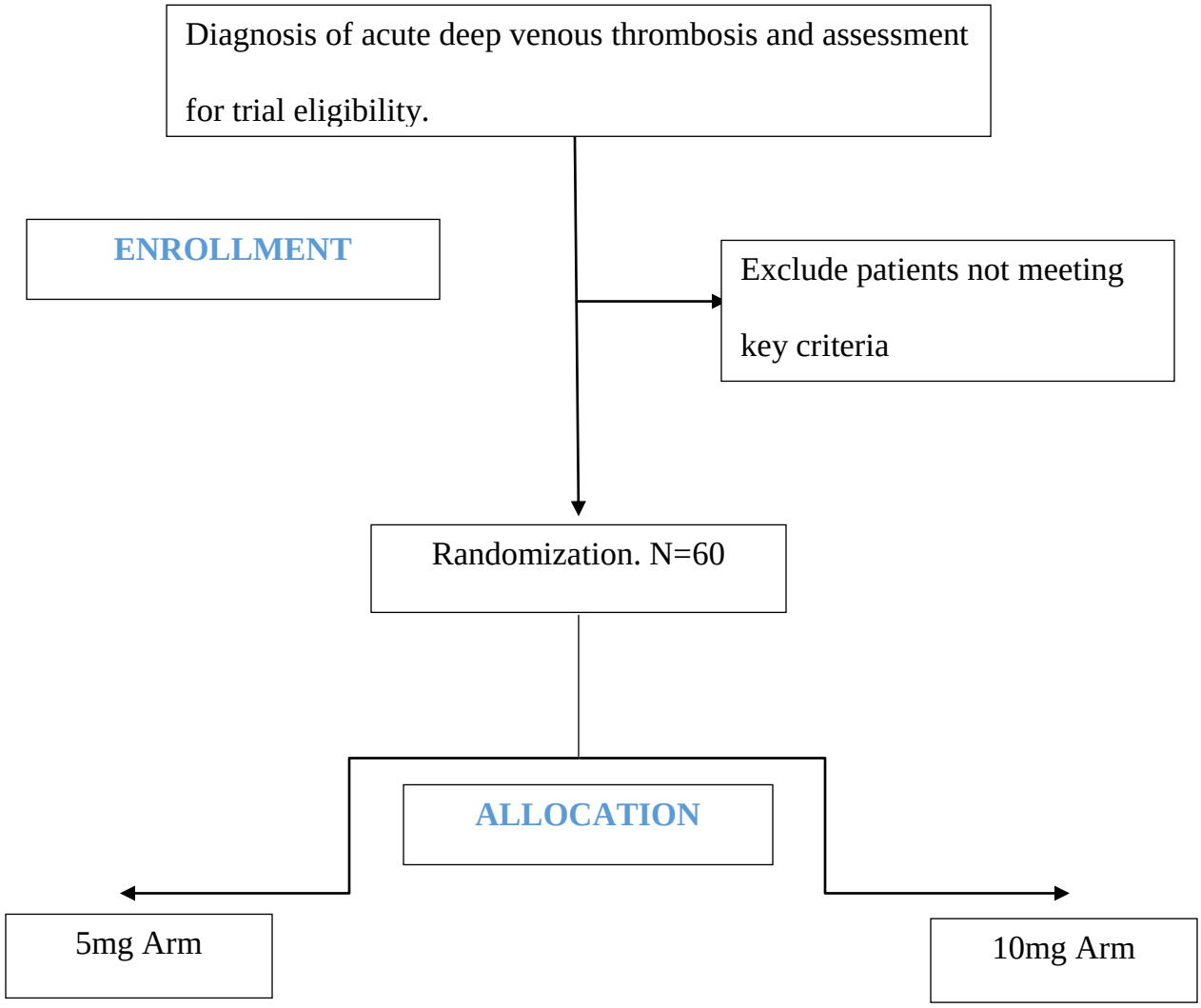
Follow up:

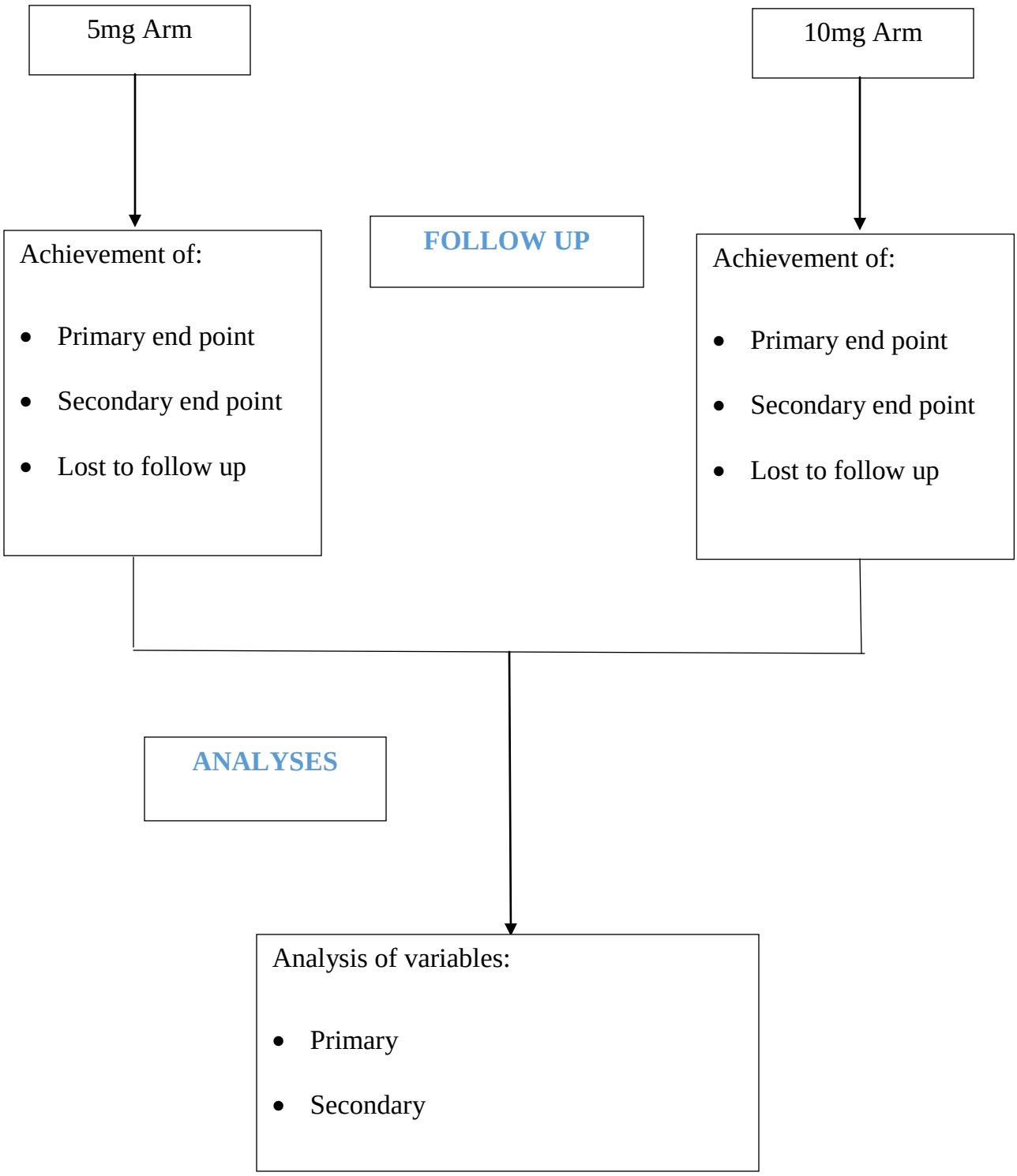
Both arms were followed up with daily testing of INR from the third day onwards. Further doses were also adjusted by the treating clinician based on the INR values. Follow up was completed when they recorded two consecutive INR values between 2 and 3. Primary outcome recorded was time to therapeutic INR, which is the number of days from initiation of treatment to achievement of therapeutic level of anticoagulation. Secondary causes to exit the trial were also recorded, such as over anticoagulation, loss to follow up, withdrawal from trial or bleeding.

Analyses:

The recorded data was analyzed with the statistical methods explained above.

Diagrammatic representation of the algorithm used:




5mg Arm
10mg Arm
Achievement of:
Primary end point
Secondary end point
Lost to follow up
FOLLOW UP
Achievement of:
Primary end point
Secondary end point
Lost to follow up
ANALYSES
Analysis of variables:
Primary
Secondary

END POINTS AND VARIABLES

Primary end point:

INR within target range of 2 -3 from two consecutive readings at least 24 hours apart. (Time measured in days). Please note that the primary outcome has already been defined as time to therapeutic INR from initiation of therapy and may or may not coincide with the primary end of trial which signifies stabilization of INR values.

Secondary end points:

1) Bleeding complications
2) Over-anticoagulation, defined as such by treating clinician.
3) Failure to achieve adequate anticoagulation despite maximum possible trial dose for three consecutive days (for such patients, treatment was planned to be changed to other anticoagulants).

Primary Variables for Analysis:

1) Arm of trial (10mg or 5mg).
2) Time in days to therapeutic INR.

Secondary Variables for Analysis:

1) Bleeding complications.

2) Over-anticoagulation.

3) Site of DVT.

4) Baseline data - INR, D Dimer value, Provoking factor, Mechanism of DVT

5) Parenteral Anticoagulant used.

6) Demographic variables – age and sex.

RESULTS

A total of 60 patients were recruited between March 2014 and August 2015, thus reaching target sample size. Thirty patients each were randomized to the two arms of 10mg and 5mg and trial data was collected. The results are presented in the order of the objectives of the trial.

RESULTS OF THE PRIMARY OBJECTIVES:

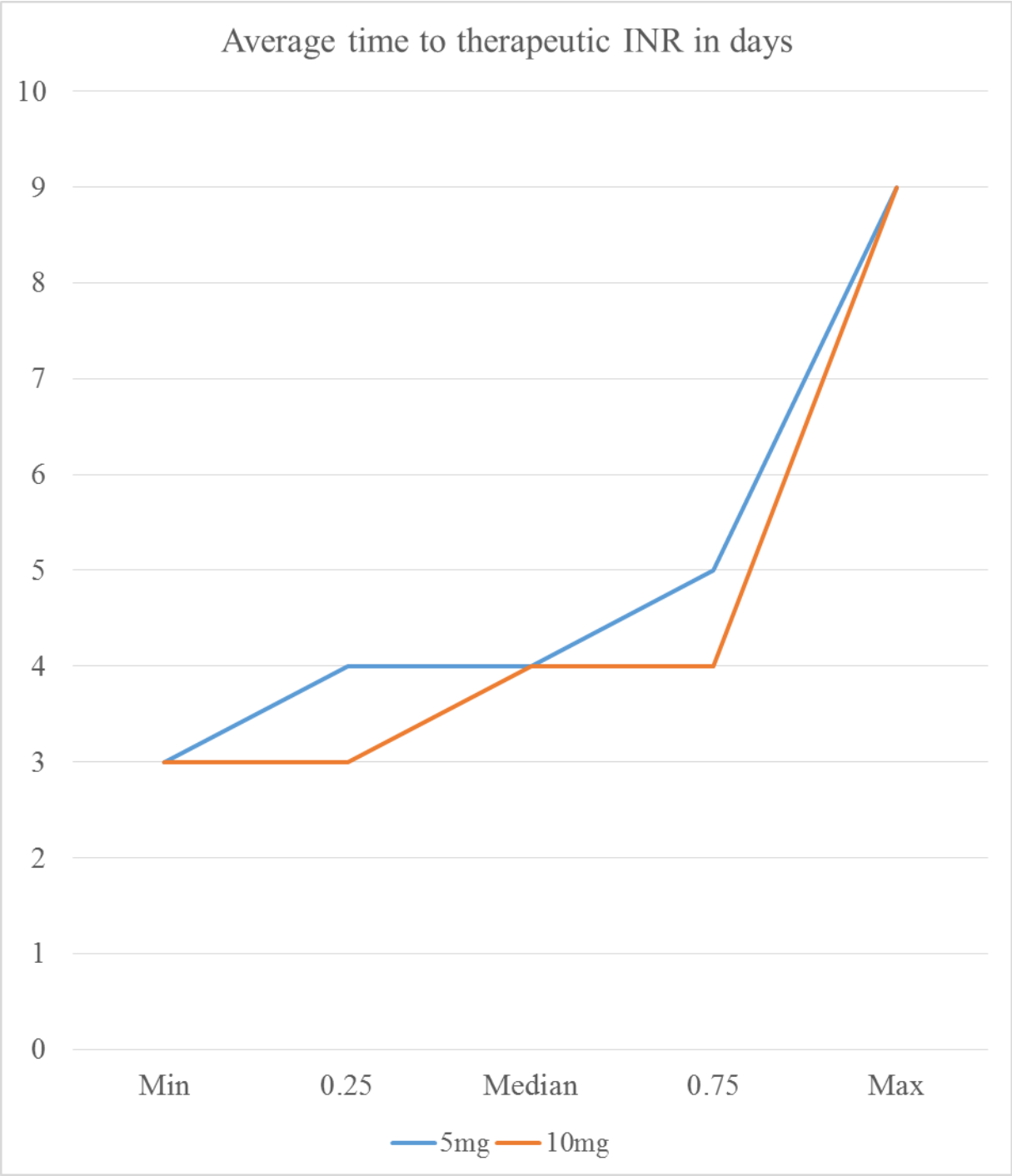
1) To determine if a 10mg initiation dose achieves adequate anticoagulation faster than 5mg initiation dose:

While a significant number of patients did not achieve a stable INR in both arms (20 in the 5mg arm and 18 in the 10mg arm) due to various reasons described below, almost all patients reached the primary outcome. Therefore time to therapeutic INR was available for 29 patients in the 5mg arm and 28 patients in the 10mg arm, the other patients failing to reach adequate anticoagulation whilst enrolled on trial.

The average time to therapeutic INR was significantly lower in the 10mg arm as compared to the 5mg arm with a P value of 0.02 as shown in the table below:

Arm	**n**	**Min**	**0.25**	**Median**	**0.75**	**Max**	**P-value**
5mg	29	3	4	4	5	9	0.02
10mg	28	3	3	4	4	9	

It is interesting to note that the outlying maximal number of days to anticoagulation in both arms were a similar 9 days. The statistical difference is better described in the following chart describing the same variables:



In the same trend of assessing how quickly patients anticoagulated in each arm. We also analyzed the INR values on days 3, 4 and 5. It was noted that average INR on day 3 for the 10mg arm was significantly higher than the same for the 5mg arm with a P value of less than 0.002. There were considerably lower differences in INR on days 4 and 5 with P values of 0.08 and 0.3 respectively. This signified that while initial anticoagulation with 10mg was faster, the overall achievements of anticoagulation were similar in both groups by day 5.

This same progression is noted in the tables below:

Average INRs on day 3:

Arm	**n**	**Min**	**0.25**	**Median**	**0.75**	**Max**	**P-value**
5mg	**29**	**0.9**	**1.18**	**1.47**	**1.79**	**4.74**	**0.002**
10mg	28	1.05	1.61	1.92	2.63	6.67	

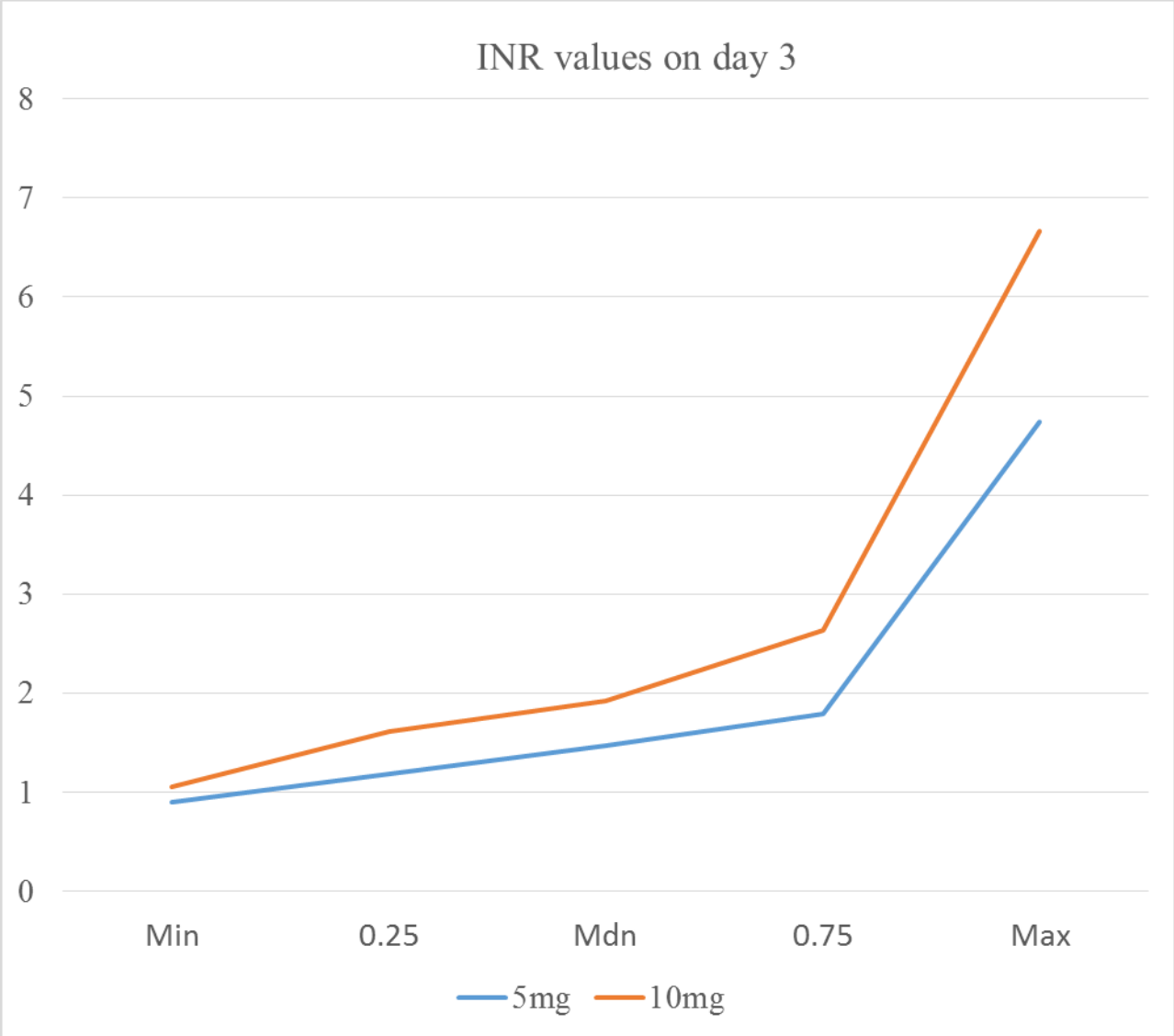
Average INRs on day 4:

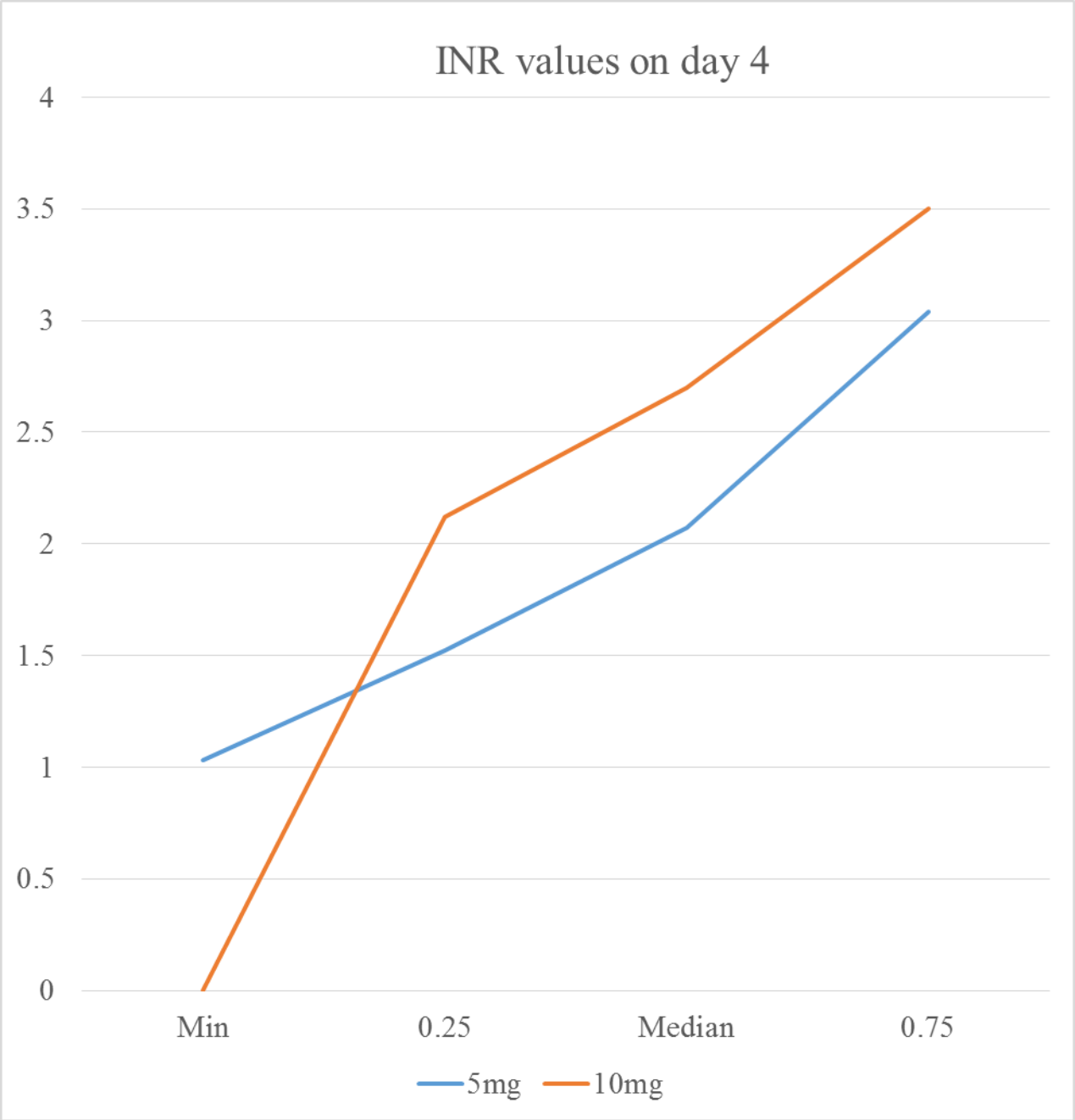
Arm	**n**	**Min**	**0.25**	**Median**	**0.75**	**Max**	**P-value**
5mg	**28**	**1.03**	**1.52**	**2.07**	**3.04**	**10**	**0.08**
10mg	28	0	2.12	2.7	3.5	8.5	

Average INRs on day 5:

Arm	n	Mean	S.D.	P-value
5mg	29	3.01	2.33	0.3
10mg	25	2.41	1.86	

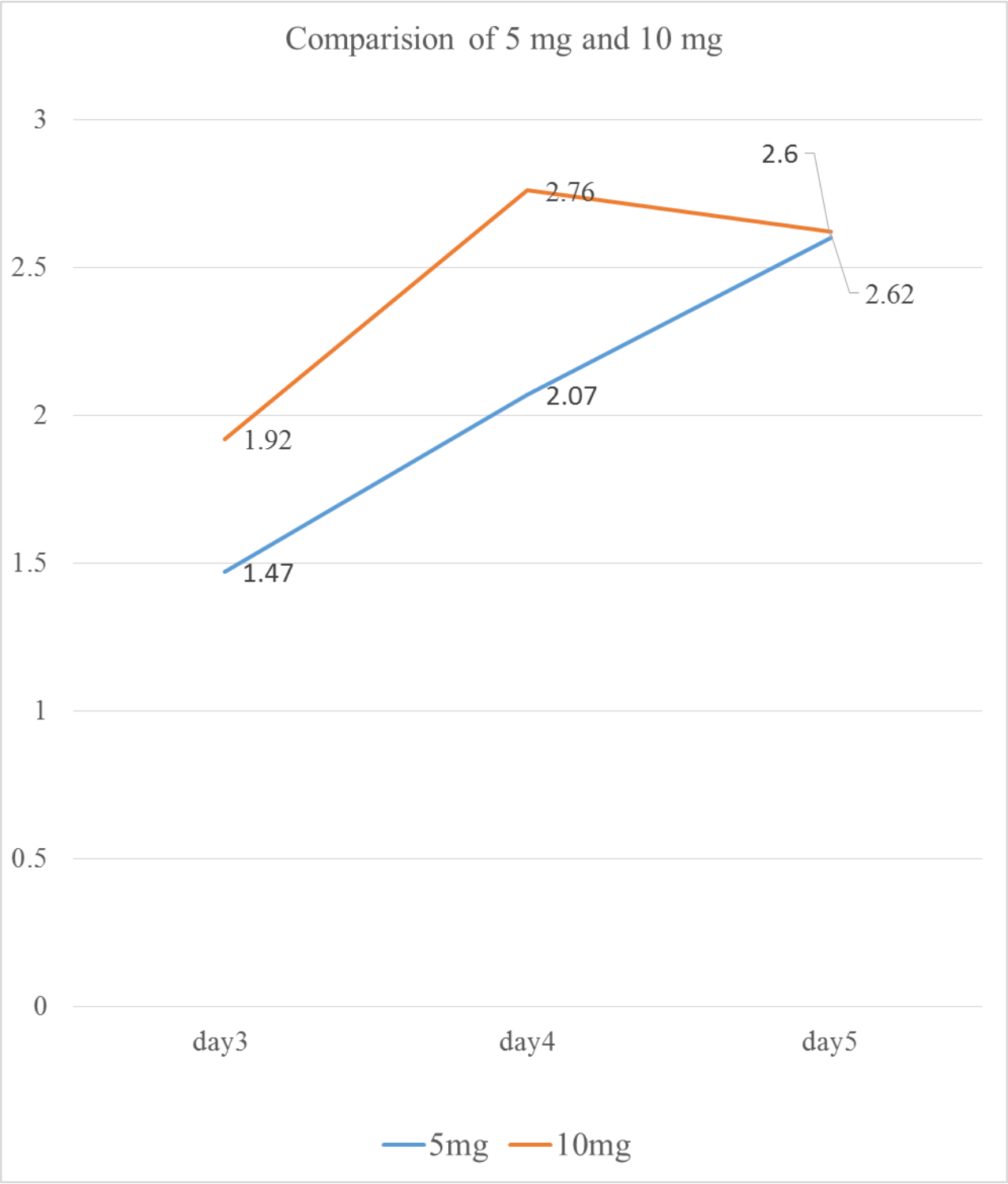
This above relationship is easier to comprehend when illustrated as below:





The overlapping lines in the above table show how the statistical difference between the two groups is coming down by day 4. By day 5 the difference in the level of anticoagulation is minimal, as shown above with the P value of 0.3.

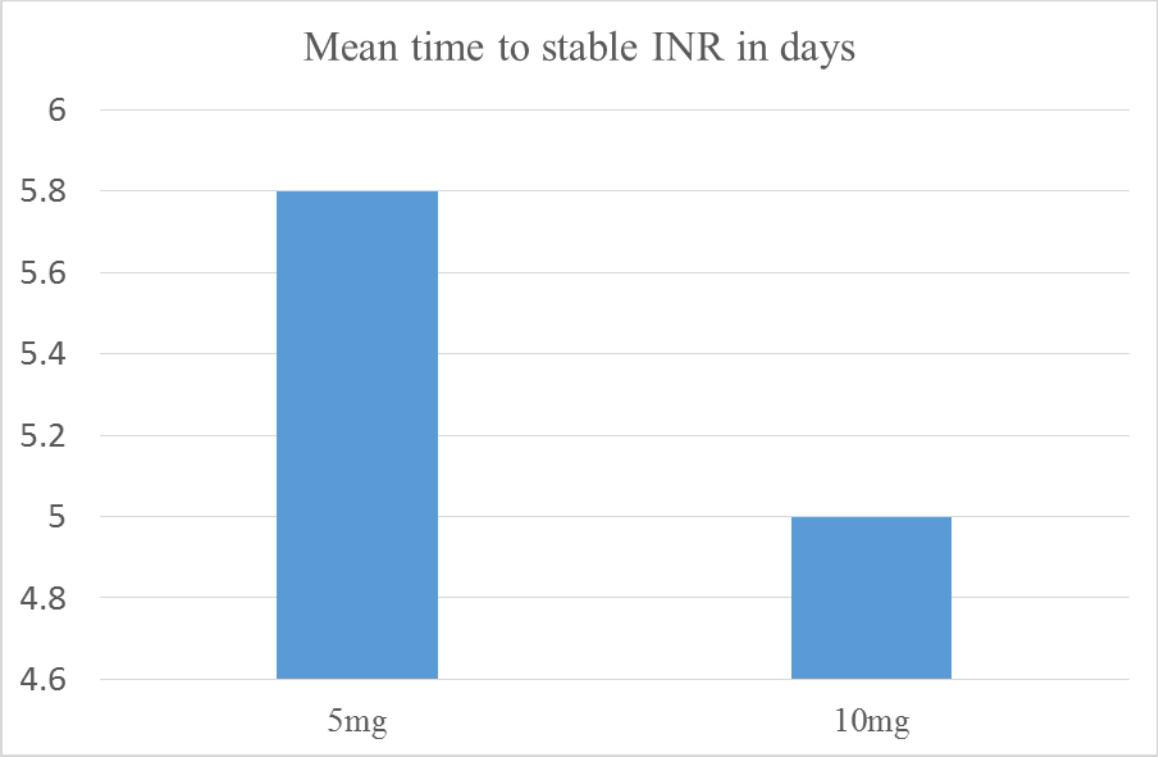
Overall the results showed that by day 5 both arms had similar levels of anticoagulation as illustrated below:



The time taken to achieve a stable INR was far more difficult to assess, due to need for longer durations of daily INR testing and significant logistical difficulties associated with the same. The available data is listed below:

Group	Observations	Mean (days)	Standard deviation	P-value
5mg	10	5.8	1.75119	0.37
10mg	12	5	2.296242	

It can be noted at this point that while there was no significant differences in the means noted above, the 10mg arm had a shorter overall timeas illustrated below –



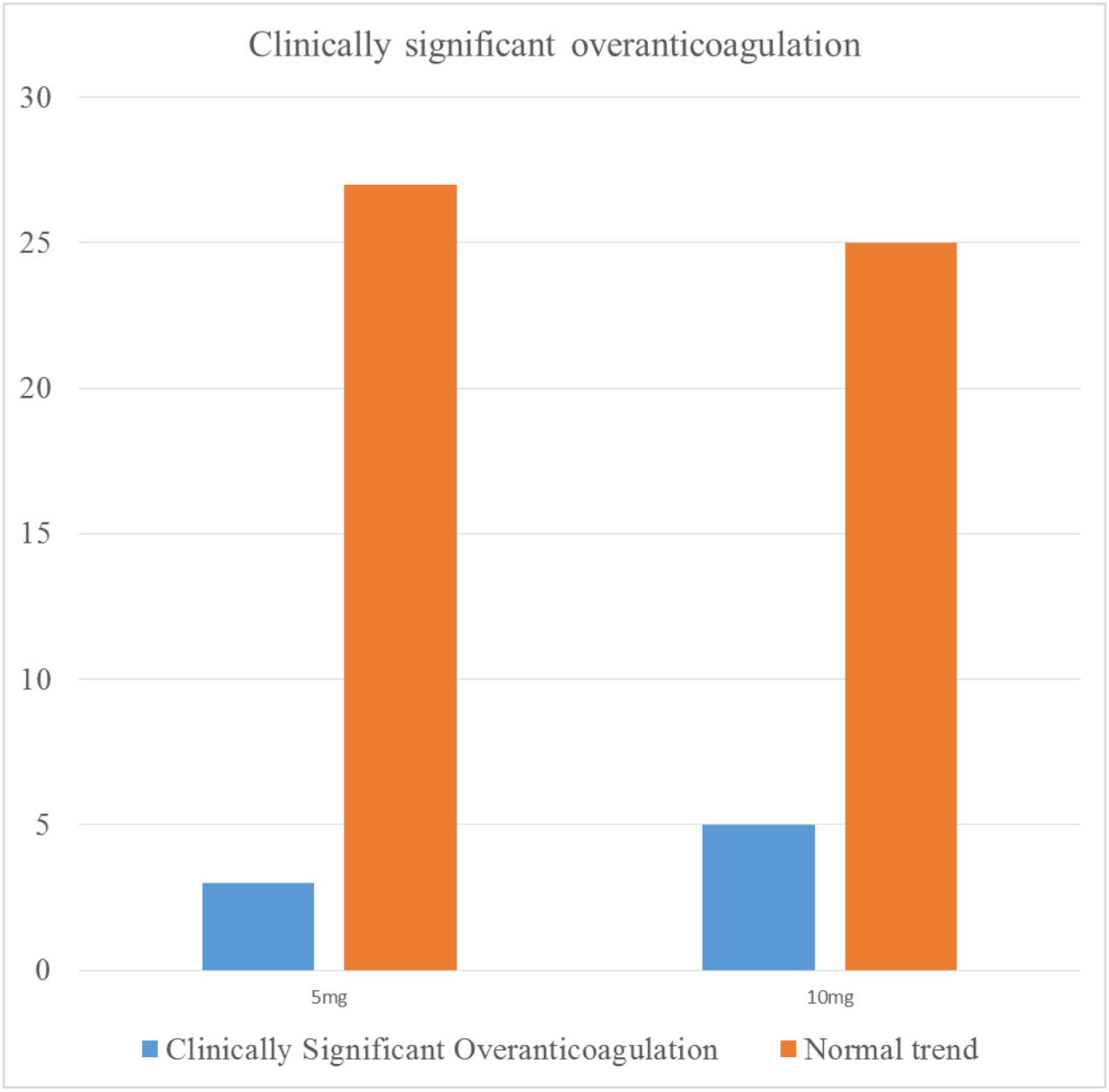
2) To determine if the 10mg initiation dose achieves adequate anticoagulation safely.

The safety of anticoagulation is primarily determined by the occurrence of major or life threatening complications requiring reversal of anticoagulation, blood and blood product transfusion and/or vitamin-K therapy. No patient whilst recruited on the trial had a significant bleeding episode during the study period. However one patient in the 10mg arm had significant bleeding the day after reaching end of trial with target primary outcome. The patient was a known to have dysfunctional uterine bleeding and compliance therapy of the same was inconsistent. We were unable to determine if the bleeding was a consequence of sudden withdrawal of estrogen therapy. Even including this patient as a bleeding complication, there was no significant difference between the two arms.

For the purpose of this analyses we decided to attempt to assess relevant anticoagulation by 'overshot' INRs of more than 3 on the third day of trial (The assumption being that if the INR is already past the therapeutic range on the first day of follow up, the patient has clearly over-responded to therapy and is headed for over-anticoagulation.). There was however not enough data to perform any statistical analyses, due to very low overall rates. The same is presented in the table below:

Arm	**n**	**Mean**	**Standard Deviation**
5mg	2 out of 30	4.3	0.62
10mg	4 out of 30	4.2	1.68

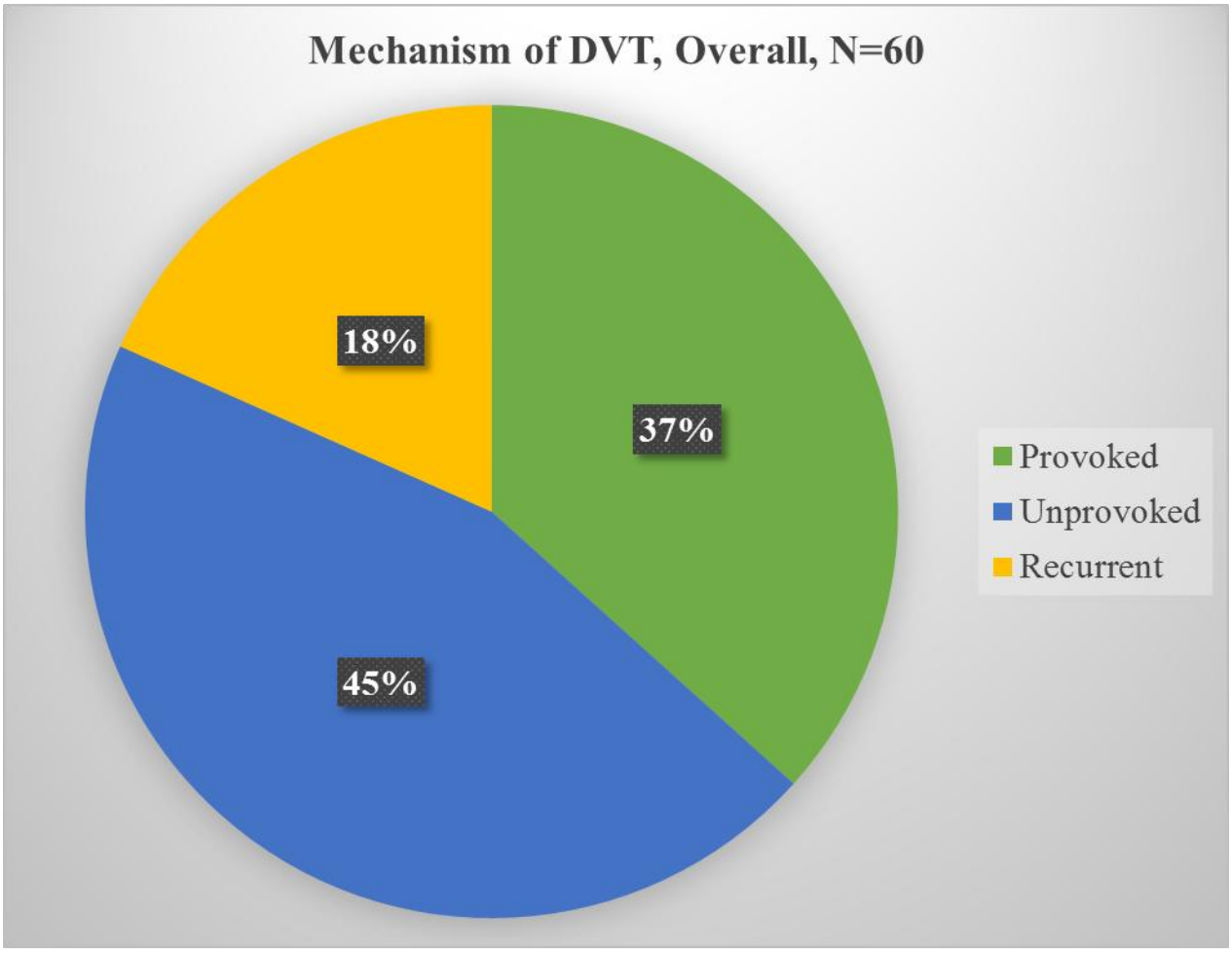
Additionally 3 patients in the 5mg arm and 5 patients in the 10mg arm were taken off trial by the clinician for concerns with over-anticoagulation. However none of these patients had clinically significant bleeding. Therefore it was safe to assume that overall risk of bleeding noted was low. This data is illustrated below.



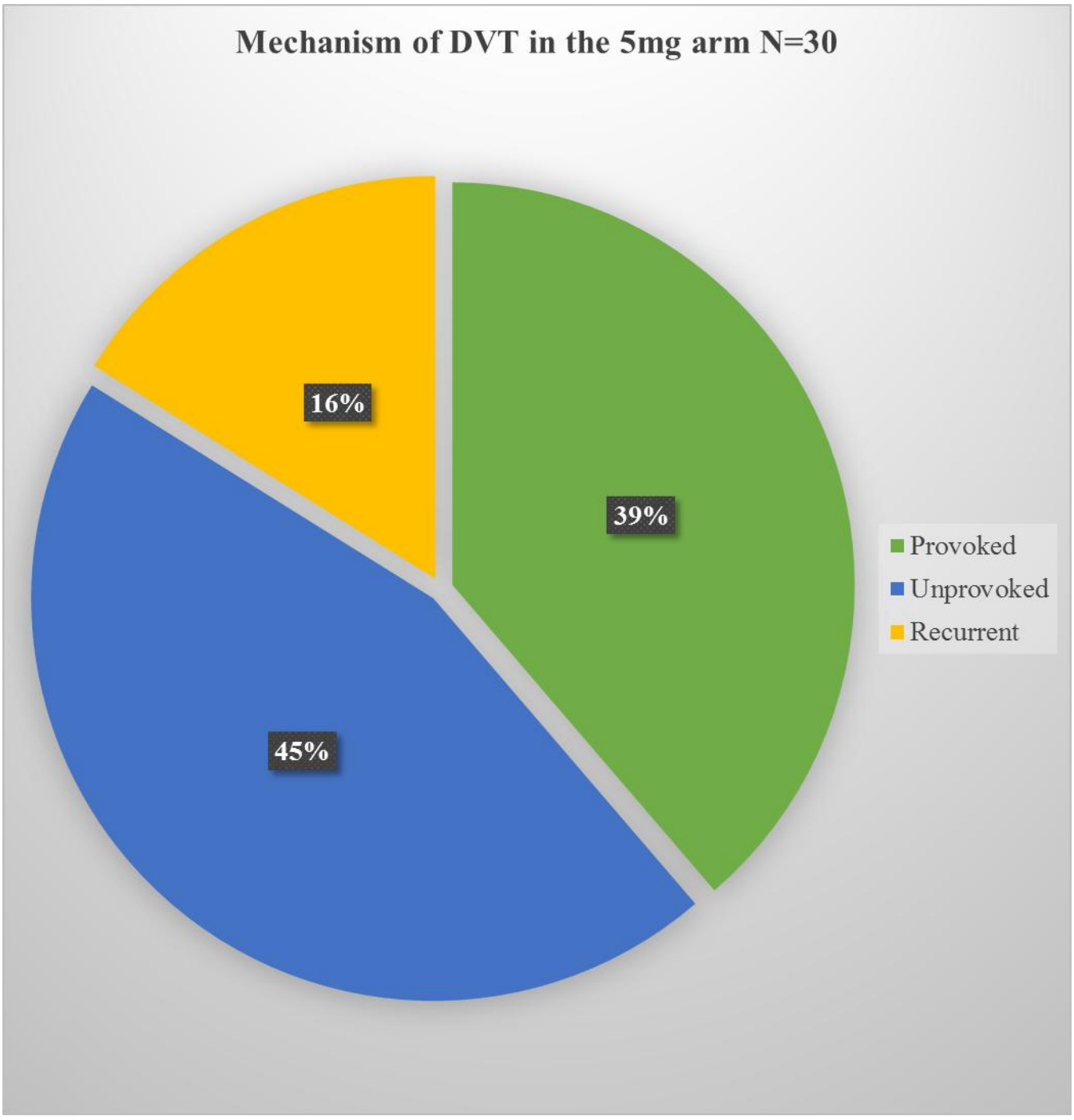
RESULTS OF THE SECONDARY OBJECTIVES:

1) To assess the clinical profile of patients presenting to our institution with deep venous thrombosis –

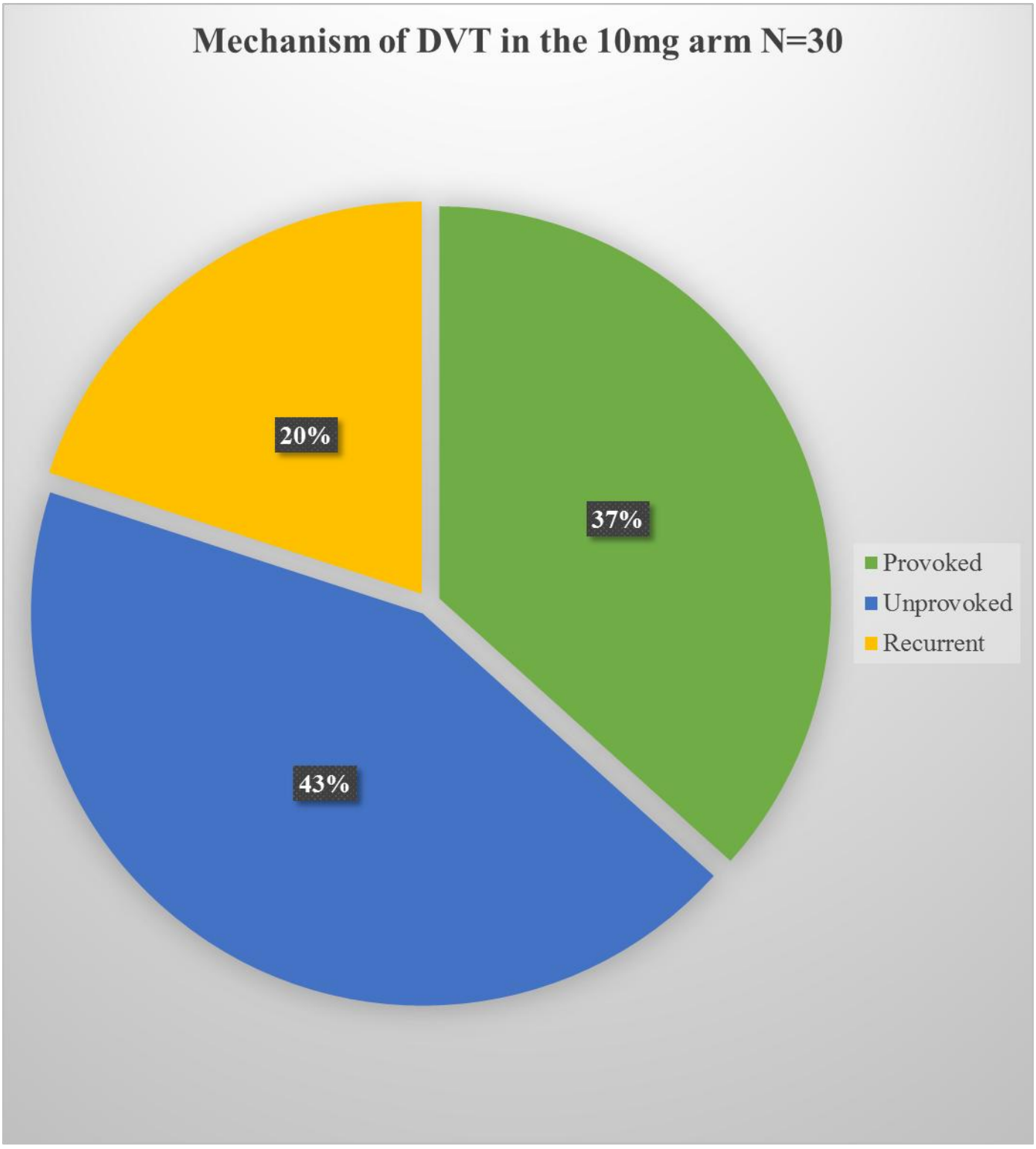
This data was collected in the clinical data form. All cases were classified according to the mechanism of deep venous thrombosis resulting in the disease. Cases presenting as recurrent acute deep venous thrombosis were recorded separately. Overall there were 22 cases of provoked deep venous thrombosis, 27 cases of unprovoked deep venous thrombosis and the last 11 were recurrent deep venous thrombosis as illustrated below.



Arm specific data are illustrated below, with the different rates in the 5mg arm:

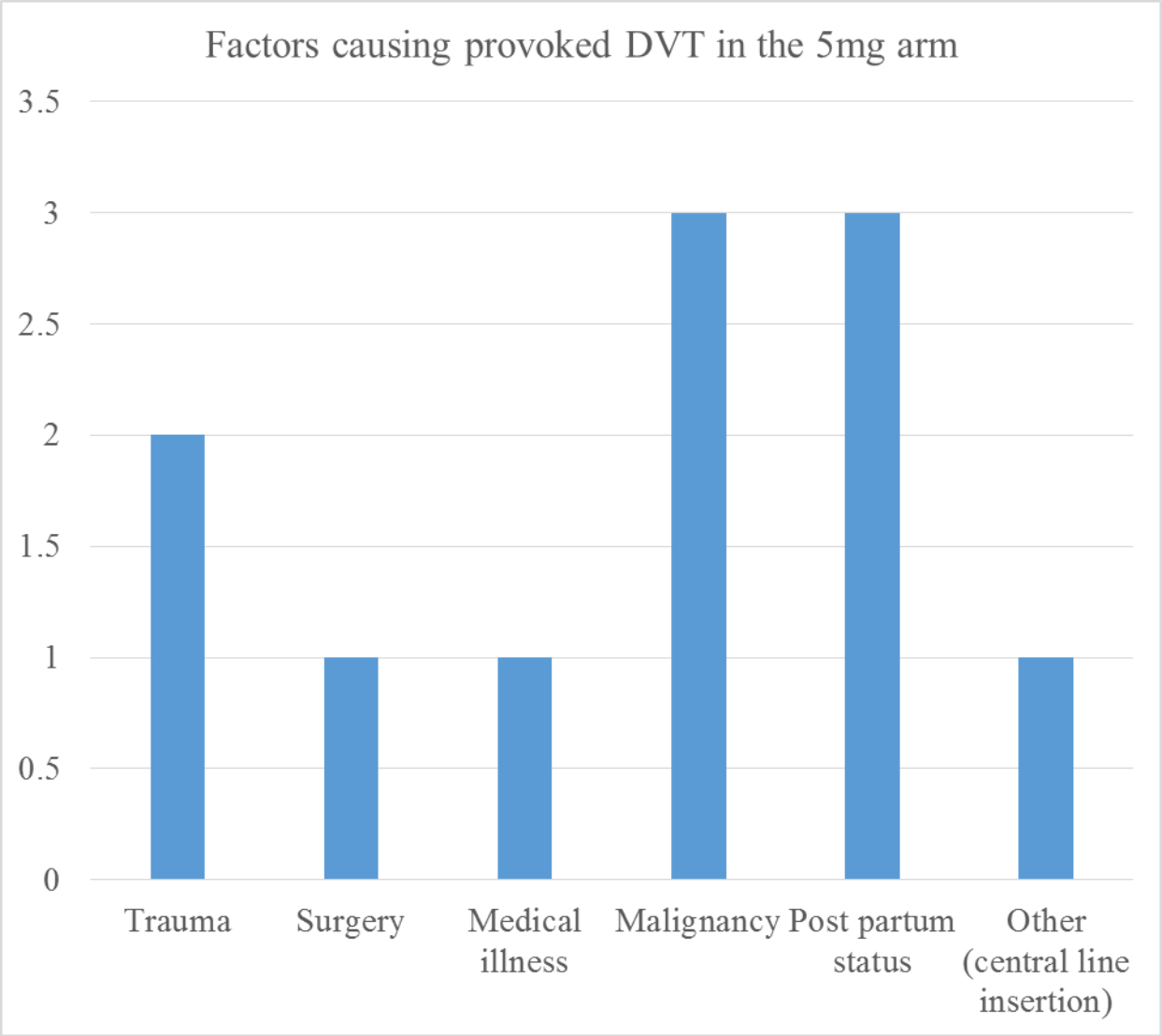


And additionally, a very similar distribution of cases was noted in the 10mg arm as noted in the chart below. Thus documenting the effectiveness of randomization.

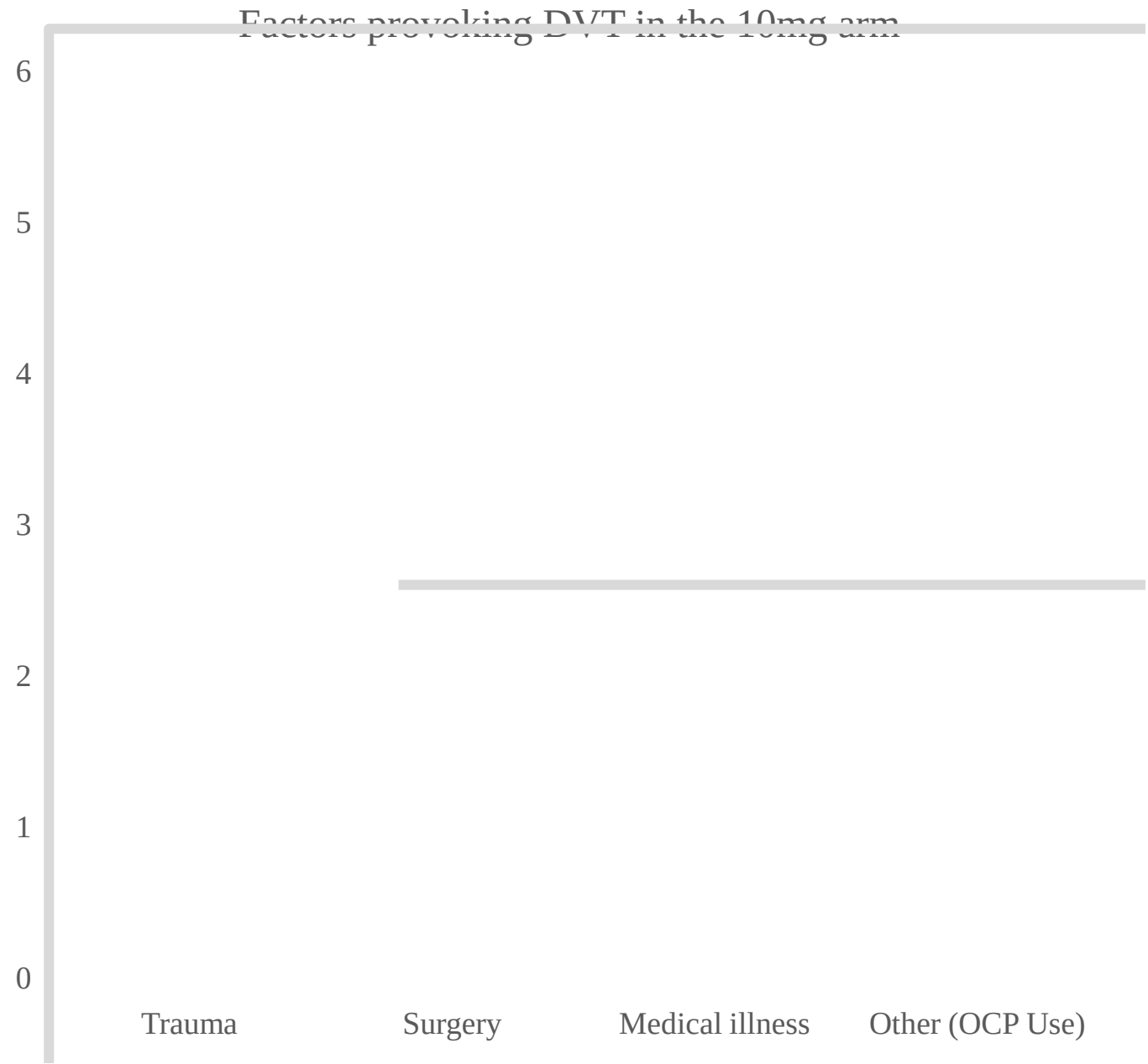

Mechanism of DVT in the 10mg arm N=30
20%
37%
43%
Provoked
Unprovoked
Recurrent

As is evident from the above charts, there was no statistical difference among the two groups allowing for normal analyses.

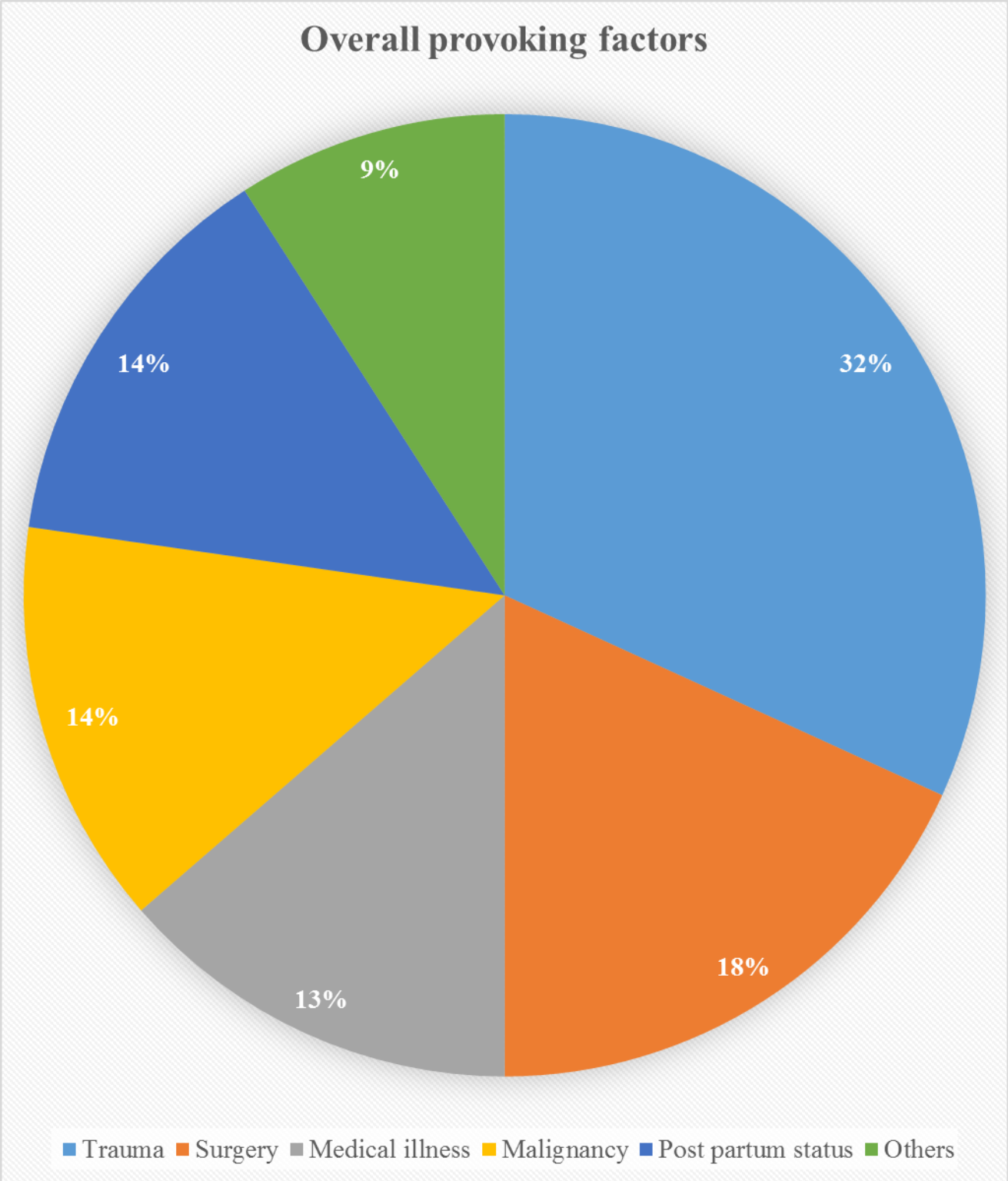
Various entities were identified to be the underlying provoking factors in the recruited patients. Provoking factor was recorded for all 23 patients whose mechanism was recorded as provoked. The different factors for the 5mg arm are listed in the table below:



The 10 mg arm had a slightly different distribution as noted below:

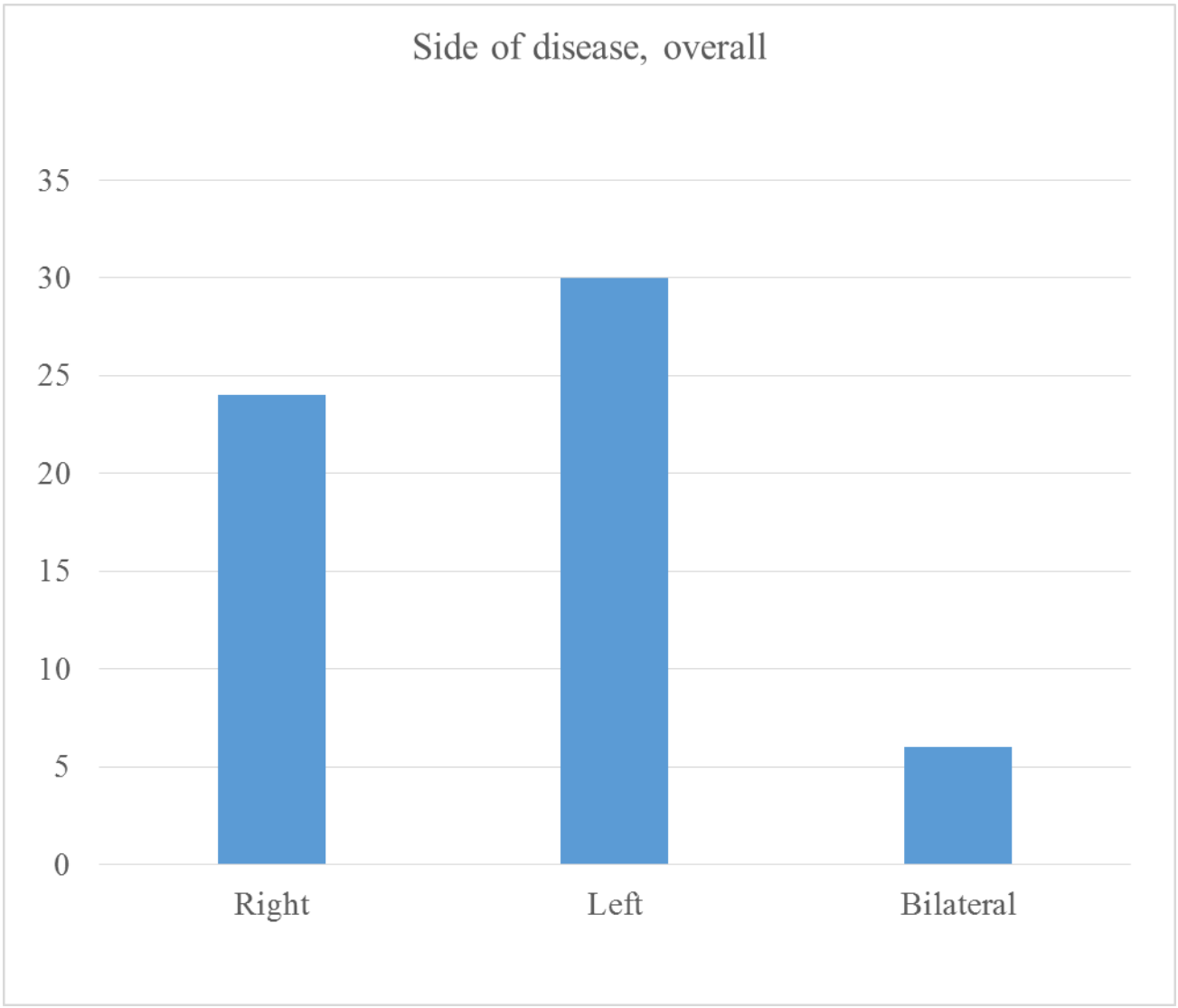


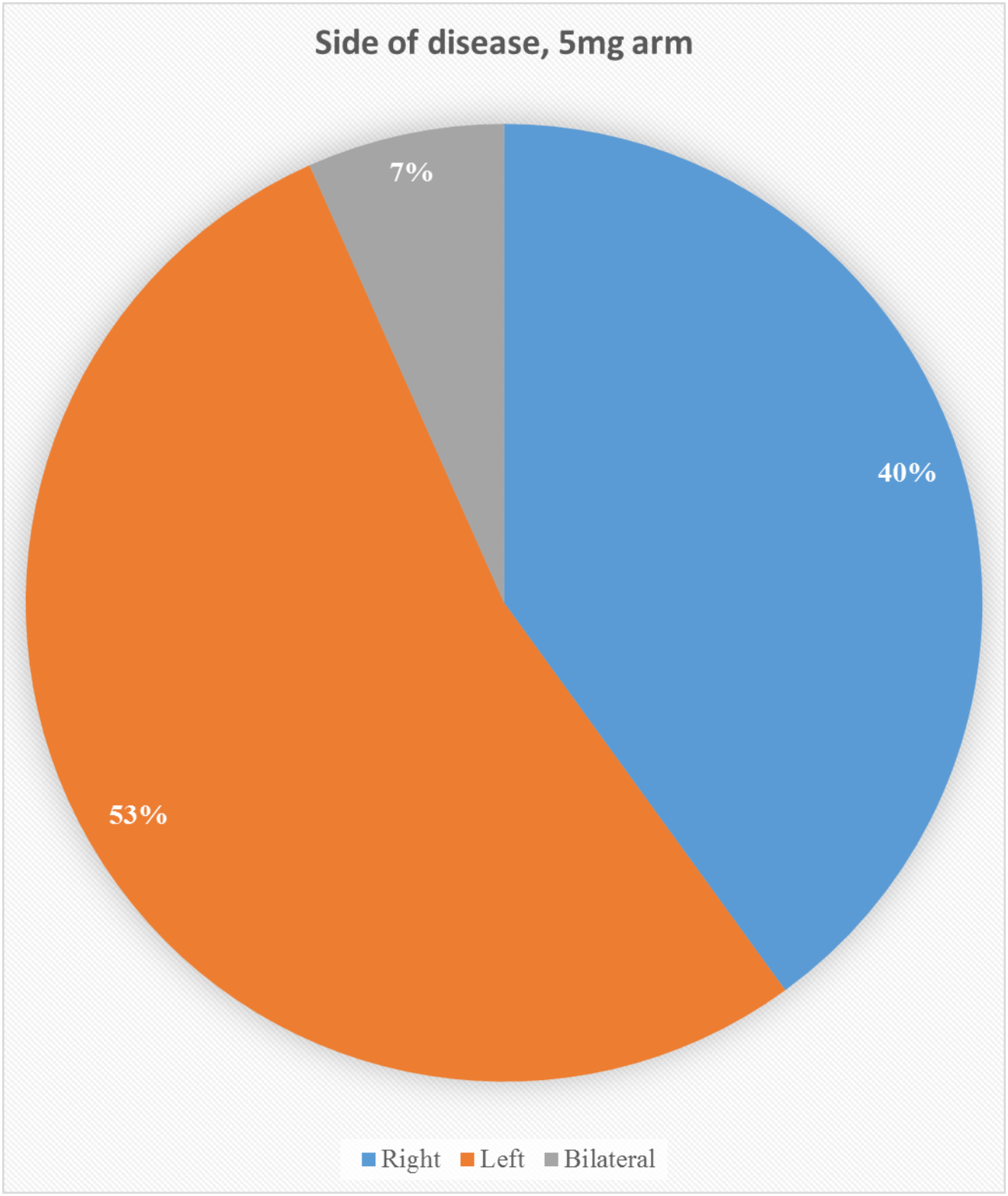
The overall distribution of provoking factors is illustrated below:

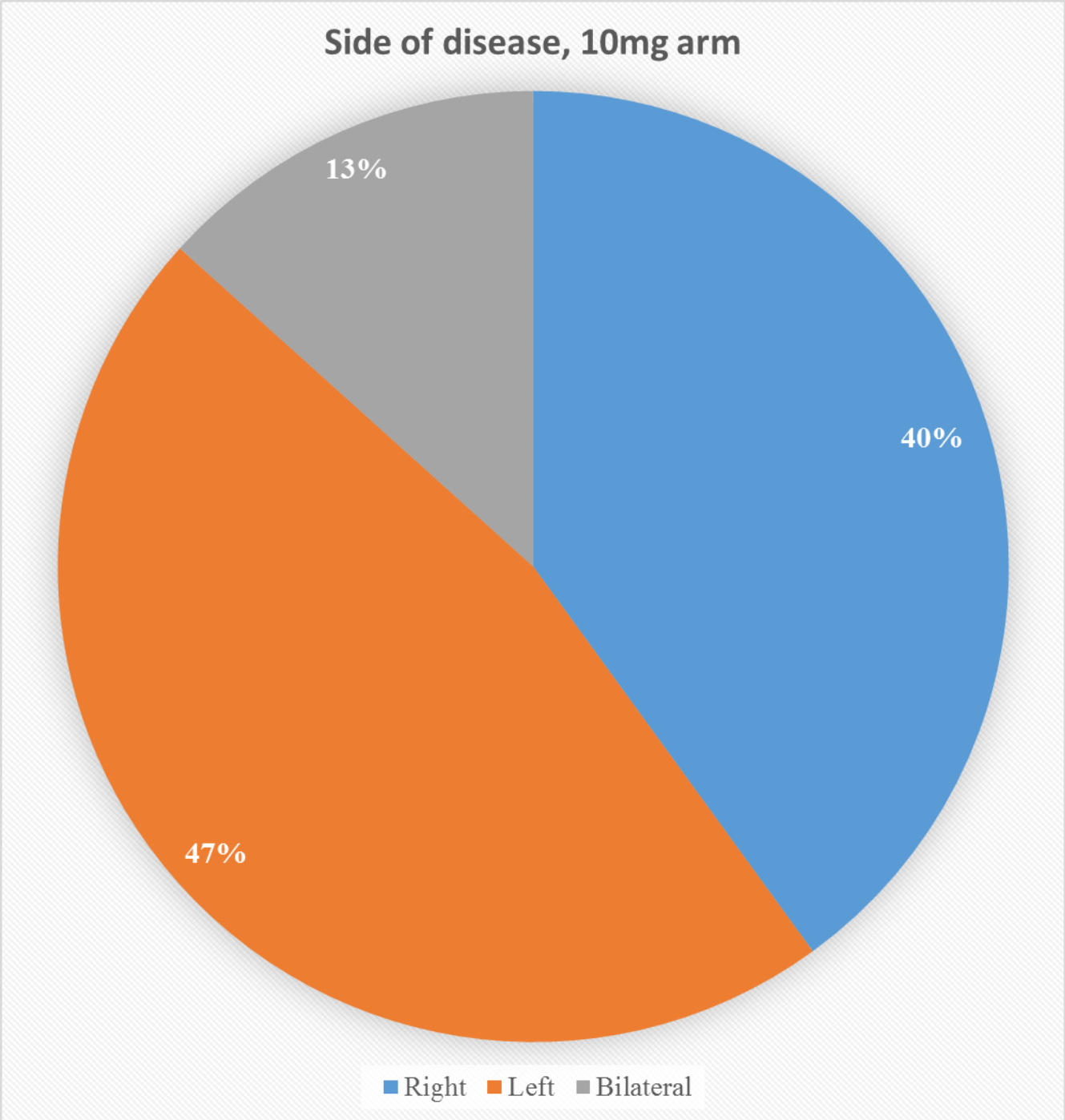


The various sites of deep venous thrombosis were recorded based on two different parameters –side and venous site. The first, more obvious and easier to assess was the physical side of disease. Accordingly patients were classified as having right, left or bilateral disease. Overall, 24 patients had right sided disease, 30 patients had left sided disease and 6 patients had bilateral disease, as illustrated below:

The differences among the two trials arms are illustrated below:




Side of disease, 5mg arm
7%
40%
53%
Right
Left
Bilateral



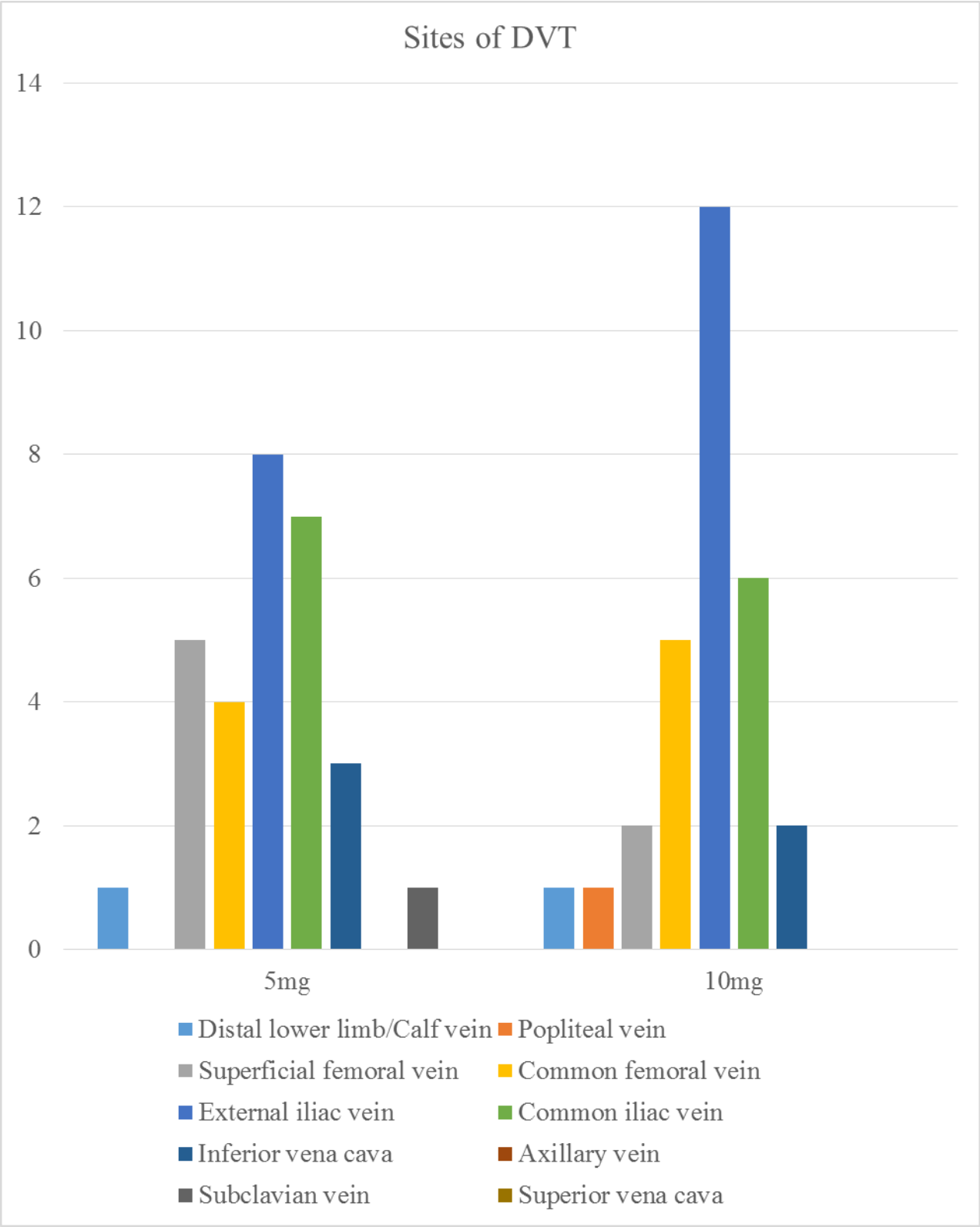
The above two tables clearly demonstrate that there was no significant difference between the two groups at all, further demonstrating the effect of randomization.

The sites of deep venous thrombosis were recorded by noting the most proximal segment of vein involved as evaluated by compression ultrasonography. Accurate data for this variable was available only for 58 patients, with one patient each in both arms not having undergone a sonological examination at our center and record of investigation done elsewhere unavailable.

The various sites were classified as distal lower limb, popliteal vein, superficial femoral vein, common femoral vein, external iliac vein, common iliac vein, inferior vena cava, axillary vein, subclavian vein and superior vena cava. The various sites recorded are listed in the table below –

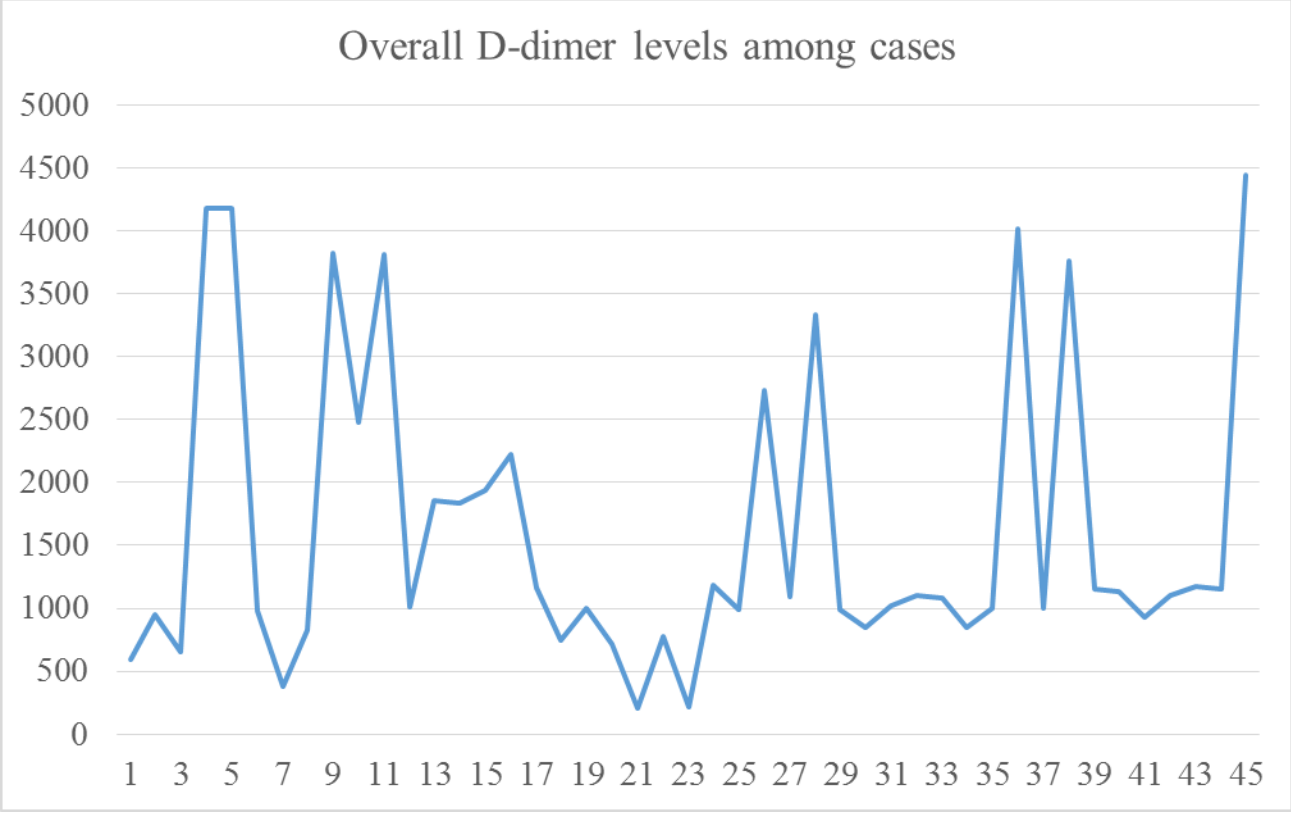
Site of Disease/Arm of trial	**5mg**	**10mg**
Distal lower limb/Calf vein	1	1
Popliteal vein	0	1
Superficial femoral vein	5	2
Common femoral vein	4	5
External iliac vein	8	12
Common iliac vein	7	6
Inferior vena cava	3	2
Axillary vein	0	0
Subclavian vein	1	0
Superior vena cava	0	0

The data is illustrated below:

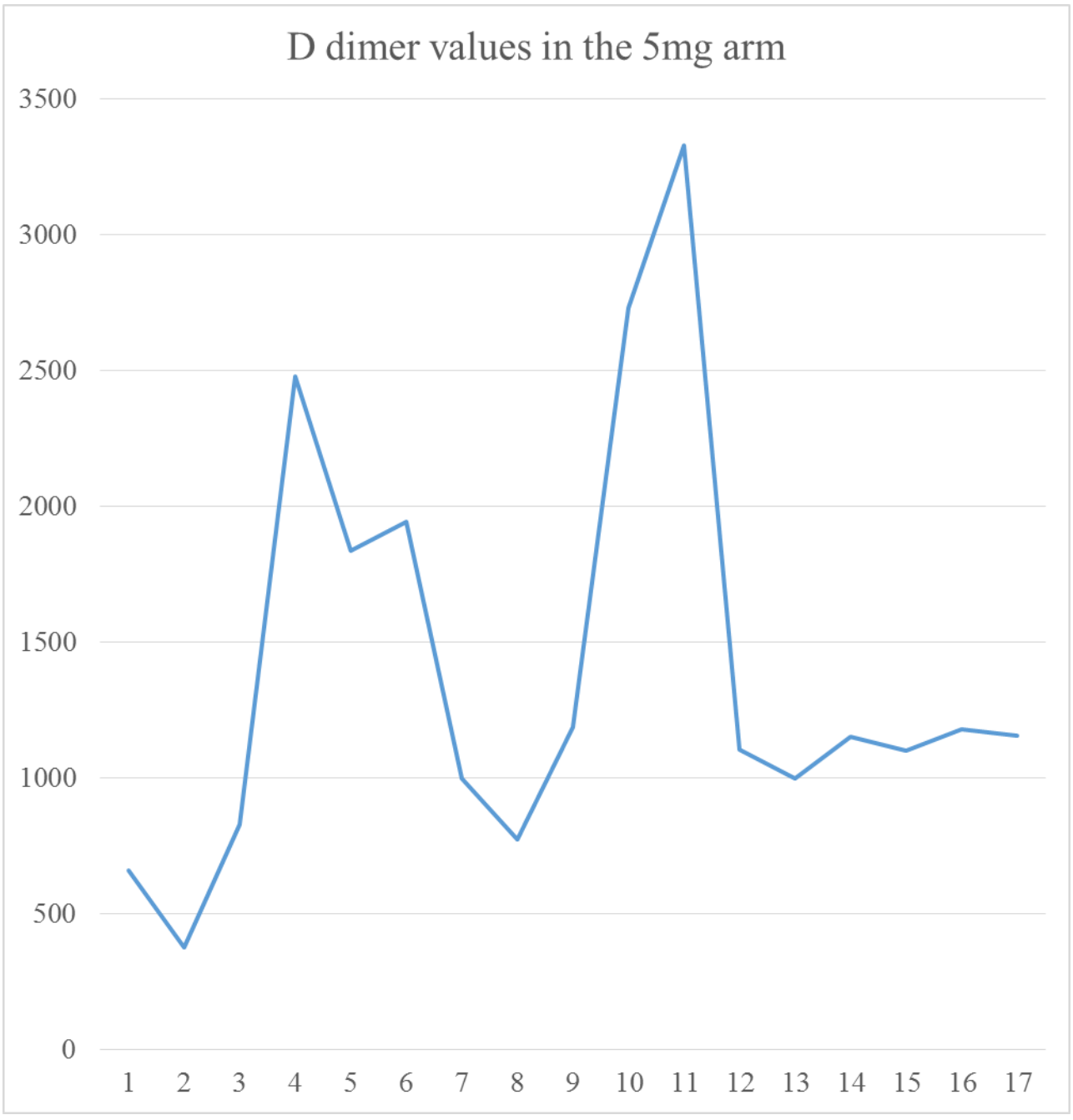


It is evident from the above data that the maximum number of cases tend to occur in the external iliac vein. The pattern of distribution remains fairly constant, except for the outlying sole case of subclavian vein thrombosis (due to central venous catheter) and the differences between superficial and common femoral vein distribution among the two groups.

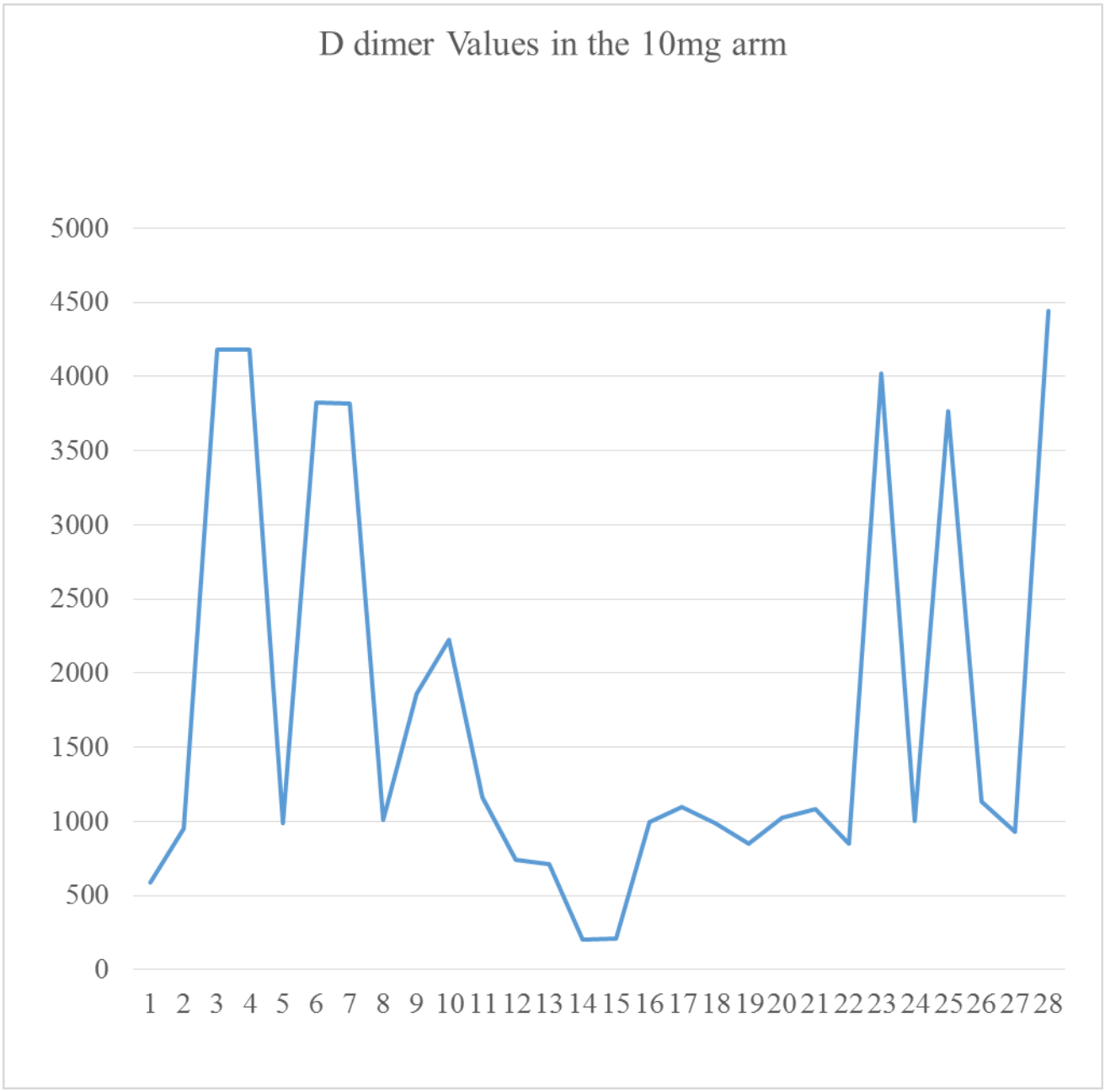
The D Dimer assay was only carried out in 45 out of the sixty patients. 28 of these 45 were allocated to the 10mg arm and the remaining seventeen to the 5mg arm. The average pattern of distribution for the overall trial is illustrated below in the following chart:



The values ranged from 212 to 4436 units. The following charts illustrate the differences in D dimer values in both arms of the trial –



Here follows the data from the 10mg arm –



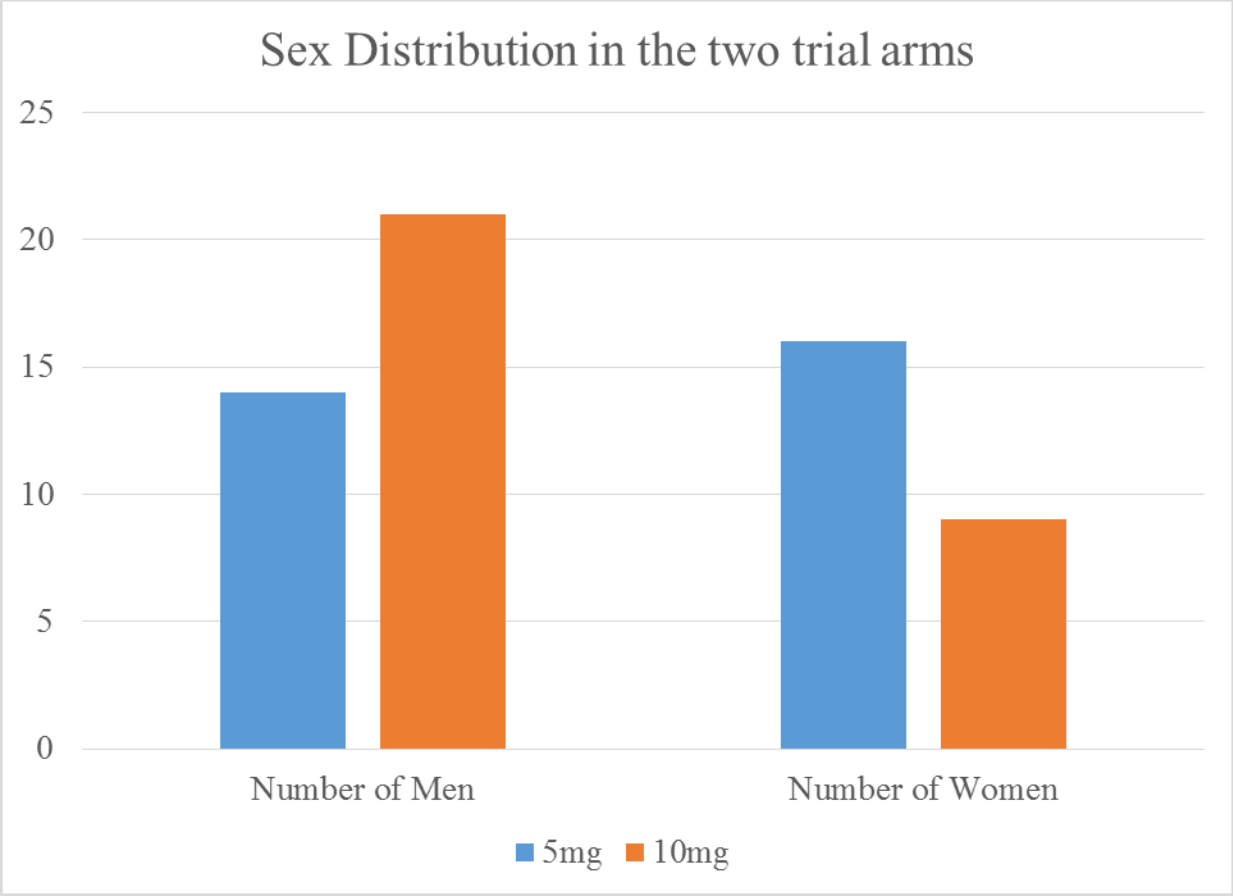
2) To obtain basic demographic variables of age and sex

These basic values were collected with the initial patient information sheet and recorded.

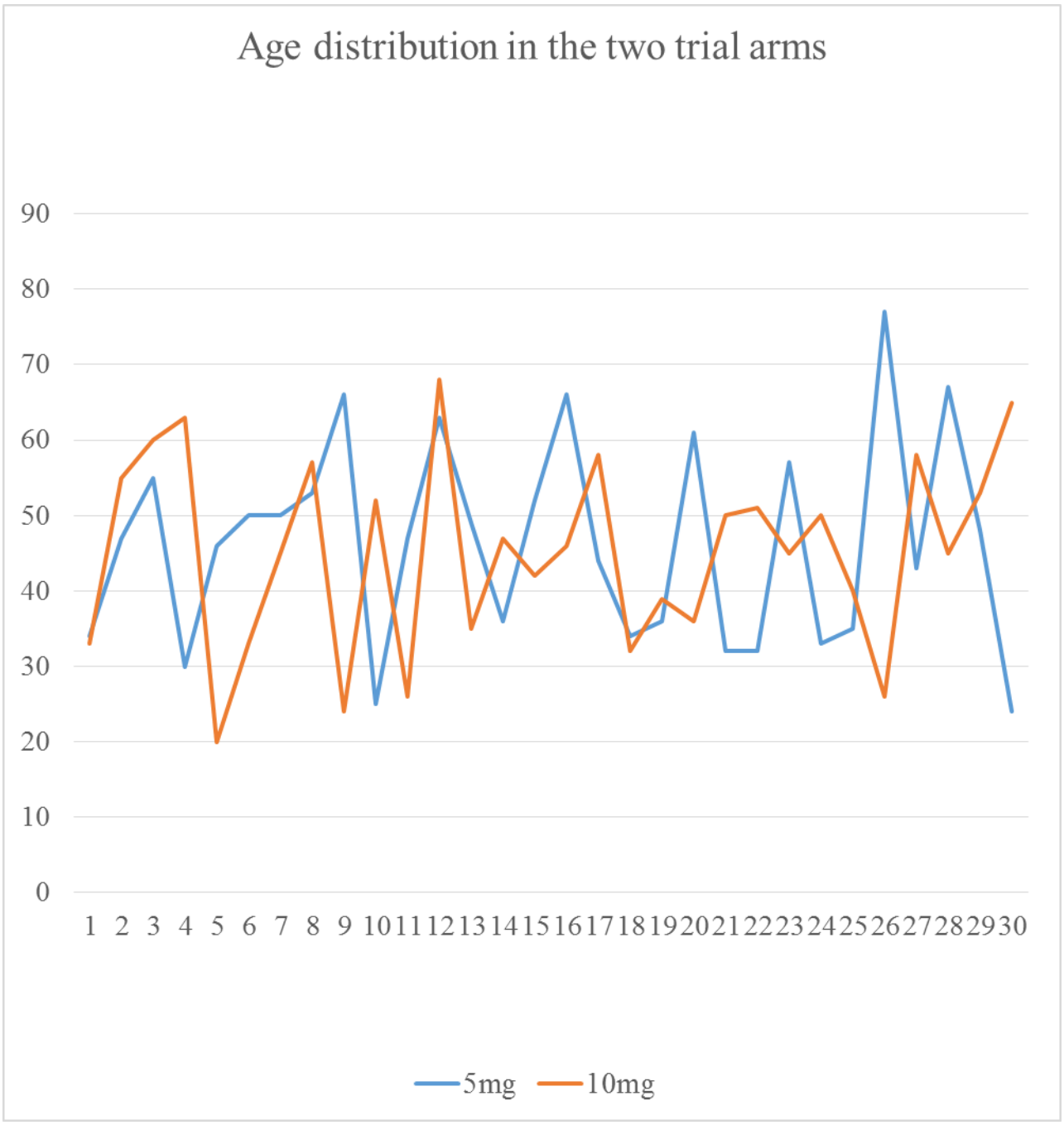
Out of the sixty patients recruited a total of 35 were men and 25 were women. However, despite randomization the strength of each sex in both arms was skewed, albeit not being significant enough to warrant a control measure.

Arm of trial	Number of Men	Number of Women
5mg	14	16
10mg	21	9
Total	35	25

This data can easily be understood by the following chart:



Age distribution among trial patients was wide in range. The youngest patient was 20 years old and the oldest was 77 years old. The pattern of age distribution among both arms of the trial is illustrated in the chart below:


Age distribution in the two trial arms
90
80
70
60
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
5mg
10mg

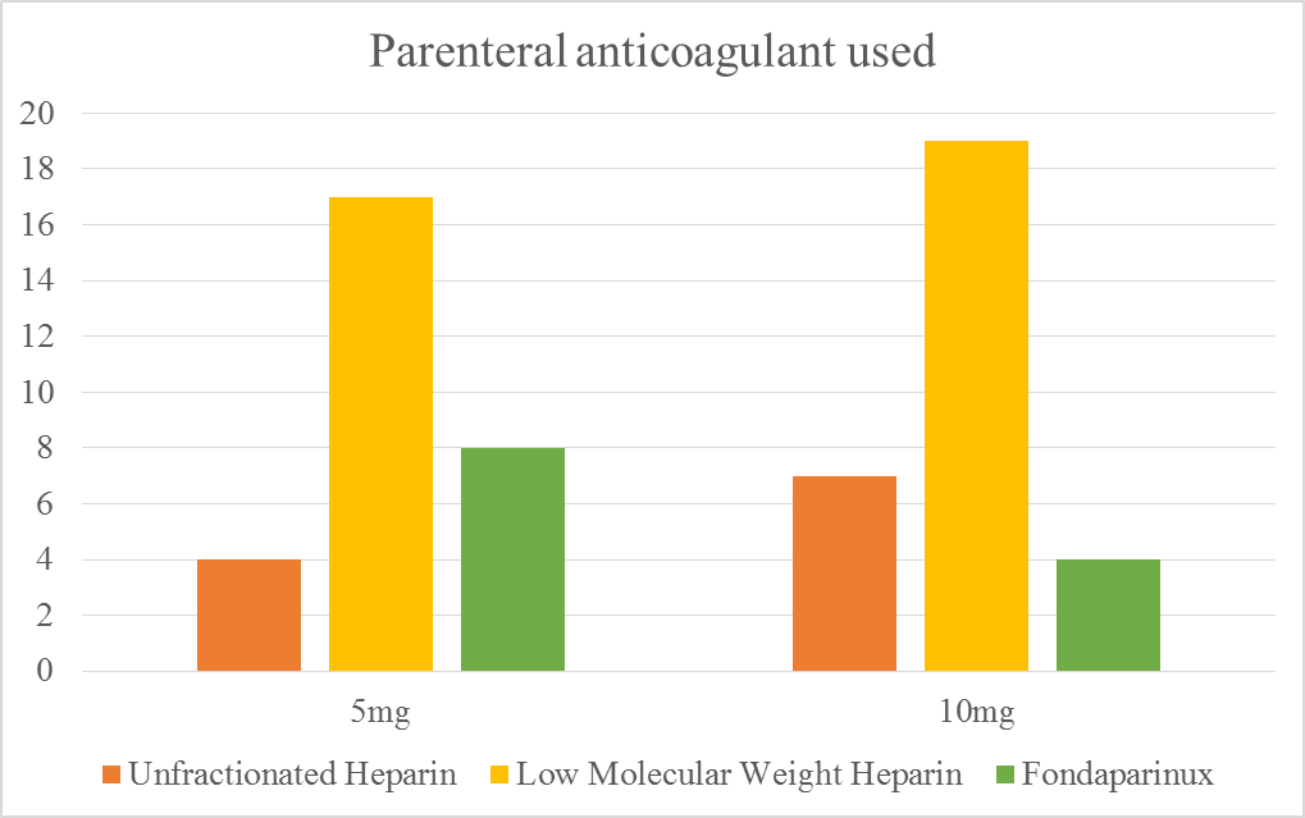
3) To assess the parenteral anticoagulant used for the overlap period:

All patients enrolled in the trial were initiated with parenteral anticoagulation as a "bridge" to the achievement of adequate anticoagulation via the oral drug. The patients were initiated on one of three agents –

1) Unfractionated Heparin
2) Low Molecular Weight Heparin
3) Fondaparinux

The usage of these agents and the distribution among both arms of the trial is documented and illustrated in the following table and chart. This data was unavailable for a single patient in the 5mg arm. The remaining 59 patients had complete data as shown below:

Parenteral anticoagulant used	**Unfractionated Heparin**	**Low Molecular Weight Heparin**	**Fondaparinux**
5mg Arm	4	17	8
10mg Arm	7	19	4
Total	11	36	12


Parenteral anticoagulant used
20
18
16
14
12
10
8
6
4
2
0
5mg
10mg
Unfractionated Heparin
Low Molecular Weight Heparin
Fondaparinux

DISCUSSION

The primary objective of this randomized trial was to determine if a 10 mg initiation dose achieves adequate anticoagulation faster than 5 mg initiation dose in the treatment of acute deep venous thrombosis, while maintaining the same safety and efficacy levels. Analyzing the speed of anticoagulation, it must be noted that with the significantly lower amount of time required to achieve therapeutic levels of anticoagulation noted in the 10mg arm as compared to the 5mg arm (P value <0.02) as described above, the primary objective of this trial was successfully met. This finding is similar to data from both the Kovacs 2003 and Farahmand 2011 trials (Farahmand et al., 2011; Kovacs et al., 2003) both of which similarly concluded that the 10mg initiation dosage led to faster therapeutic anticoagulation. The significance found in the Kovacs 2003 trial was greater than ours at 0.001. However Kovacs et al also found that there was a significantly higher number of patients in the 10mg group as compared to the 5mg group who had achieved a therapeutic INR by day 5 with a P value of 0.001. This finding lies in stark contradiction to the absence of significantly different rates of anticoagulation by day 5 that we have noted, with the P value between the two arms at only 0.3. Also while Farahmand et al found a significant difference in INRs on day 4 as well, our data for day 4 does not tell the same story with a P value of just 0.08.

Overall the curve of anticoagulation as described tends to meet at day 5 for both arms, and while 10mg may achieve oral anticoagulation faster, it has been argued that the 5mg

protocol is safer to use in certain special populations (Mahtani et al., 2012) wherein frailty, age and suspicion of bleeding are a significant concern. It remains to be seen whether this finding of faster anticoagulation will translate to overall clinical relevance, considering that by day 5 both arms tended to achieve adequate anticoagulation. This faster rate may however be extremely desirable when attempting to treat certain cases of deep venous thrombosis on outpatient basis. This is considering both the ease to the management systems such treatment would afford, and more importantly considering the billions of dollars in health-care costs this would be able to save (Spyropoulos and Lin, 2007).

Moving on, another area of concern remains the "time to stable INR" defined as two consecutive INR readings, within the target range of 2 to 3 and least 24 hours apart. This was considered as the primary end point for our trial and overall goal of therapy, however was only met by a low percentage of the patients studied in this trial (22 out of 60 patients). It was noted that in the patients who did reach this stable INR value, patients on the 5mg arm were on average, slower than patients on the 10mg arm by 0.8 days. However in our study this remained insignificant with a P value of 0.37.

The above data, especially in comparison to the data from the four previous trials conducted (Farahmand et al., 2011; Kovacs et al., 2003, 1999; Quiroz et al., 2006) elucidates the efficacy of the 10mg initiation dosage of Warfarin. However considering

that current clinical practices involve a usual five to seven day overlap of parenteral anticoagulation anyway (ACCP, 2012; Weinmann and Salzman, 1994) how this provides a real clinical benefit in the inpatient setting is unclear.

The additional question addressed as a primary objective was to also determine if the 10mg initiation dose achieves adequate anticoagulation safely. The main safety concern with 10mg warfarin was the possibility of major bleeding complications, despite the low to negligent rates noted in the previous trials and studies (Farahmand et al., 2011; Garcia et al., 2013; Kovacs et al., 2003, 1999; Quiroz et al., 2006). As noted in the results section, no patient had a bleeding complication while on trial, however one patient from the 10mg arm went on have significant bleeding in the immediate post trial period and warrants documentation.

As an additional assumed predictor of safety, we collected data regarding withdrawal of the patient from the trial by the treating clinician due to clinically significant anticoagulation. This was done to assess whether the clinicians were affected by the non-blinding open label nature of this trial and also to ascertain if either arm caused more clinically alarming trends of anticoagulation. The low rates of withdrawal from trial due to this reason alone left us unable to prove any statistical difference between the two arms of the trial, however 5 patients were withdrawn from the 10mg trial and 3 from the 5mg trial.

Another parameter used to assess the risk of bleeding was over-anticoagulation at day 3, defined as an INR of more than 3 on the first day of follow up testing. This was considered as a possible cause of concern and anticoagulation by 'overshot' INRs of more than 3 on the third day of trial was specifically analyzed. The assumption was that if the INR is already past the therapeutic range on the first day of follow up, the patient has clearly over-responded to therapy and is likely headed for over-anticoagulation. The rates of this parameter as noted above, were 2 out of 30 for the 5mg trial and 4 out of 30 for the 10mg trial. However, the rates were too low to allow for statistically significant analysis to be carried out.

Therefore, while there is some lingering doubt regarding bleeding due to the 10mg trial, there was no statistically higher risk of bleeding noted during the acute phase of treatment of deep venous thrombosis. This finding was consistent with the findings from the other randomized trials and reviews (Farahmand et al., 2011; Garcia et al., 2013; Kovacs et al., 2003, 1999; Mahtani et al., 2012; Quiroz et al., 2006).

The first secondary objective was to assess the clinical profile of patients presenting to our institution with deep venous thrombosis. The etiopathological basis of deep venous thrombosis was studied by recording what led to the occurrence of deep venous thrombosis. We identified if the disease was of new onset or if it was a case of

recurrence. We also noted if the disease was provoked or unprovoked, and if provoked what the specific provoking risk factor was. Overall there were 22 cases of provoked deep venous thrombosis, 27 cases of unprovoked deep venous thrombosis and the last 11 were recurrent deep venous thrombosis. The incidence rates of deep venous thrombosis range from about 25 to 50% for unprovoked deep venous thrombosis and are slightly higher for provoked deep venous thrombosis (Martinez et al., 2014; White, 2003). White et al also noted that there was a significantly high number of patients who developed venous thromboembolism as the first sign of malignancy and were mistakenly classified as unprovoked while the underlying malignancy remained undiagnosed (White RH et al., 2005).

Various risk factors have been identified to play a significant role in provoking the occurrence of a first or recurrent episode of deep venous thrombosis (Heit, 2012; Heit et al., 2002; Sharma et al., 2009; Souto et al., 2000) . The factors we noted in our study were major trauma, recent abdominopelvic or vascular surgery, significant medical morbidity, active malignancy, and postpartum status or estrogen therapy. We did not do routine pharmacogenetic testing as a baseline assessment of the individual's susceptibility to warfarin. (Larsen et al., 2003; Souto et al., 2000).

The site of deep venous thrombosis is not something that has been as extensively documented in previous trials as we have done in this study. One Japanese study attempted to understand exactly what the most common site of deep venous thrombosis is

in their patient population and found that it was the distal or calf veins (Yoshimura et al., 2012). In our study the most common site was the external iliac vein with 34% of all cases, followed by the common iliac vein and the common femoral veins. The more proximal site noted in our study is alarming, due to the well-established fact that proximal lower limb deep venous thrombosis has a higher risk of throwing an embolus (Boc et al., 2014).

We also obtained additional baseline data in the form of the D-Dimer assay value. D-Dimer values tend to be sensitive to the amount of thrombosis in the patients system, however they can be easily affected by cancer, infection or recent surgery and are not specific (Crippa et al., 1997). As clearly noted in our data, the range of D-dimer values was wide, between 212 to 4436 nanograms/ml with an overall average value of 3710.56 nanograms/ml. Our findings go on to reiterate that in the exclusion of deep venous thrombosis, D-Dimer values must be looked at in light of clinical probability of DVT (Hirsh and Hoak, 1996; Longo, 2012; Michiels et al., 2015; Wells et al., 2003) as at least two patients had values less than the conventional cut off of 500 nanograms/ml (Schouten et al., 2012) and still had confirmed deep venous thrombosis on compression ultrasonology.

The demographic variables of age and sex were also recorded and analyzed. Previous epidemiological studies have noted the higher risk of deep venous thrombosis in men

compared to women (Heit, 2015; Spencer et al., 2006), and our findings were consistent with the same, with 35 men and 25 women effected by the disease. Age was another factor noted with the average age of presentation in our study being 45.67 years. While the average incidence of venous thromboembolism as a whole is said to continue to increase with age (Heit, 2005; Spencer et al., 2006), it must be noted that less than the probable number of elderly patients affected by deep venous thrombosis were noted in this trial due to the exclusion of patients with pulmonary embolism (which also increases with age), mortality from the disease or possible lack of access to care.

Our trial did not standardize the parenteral anticoagulant used as a 'bridge' to therapeutic INR like some previous studies (Farahmand et al., 2011; Kovacs et al., 2003; Quiroz et al., 2006). Since the parenteral component of anticoagulation was beyond the scope of this trial and warfarin action was assessed with PT (INR) which is unaffected by these agents, it was decided to allow for greater clinical flexibility while recording the current practice trends in our center. Our data revealed that most patients were treated with low molecular weight heparins (36 subjects) as compared to the far more cumbersome unfractionated heparin (11 subjects) and the more expensive fondaparinux (12 subjects). Low molecular weight heparins are increasingly popular in the treatment of deep venous thrombosis, the only contention being that they cannot be used in patients with impaired renal function (ACCP, 2012; Hirsh and Hoak, 1996; Royal College of Physicians, 2012). As noted above, our data showed a similar trend.

LIMITATIONS

There were several limitations noted in the conduct of this trial. The most important limitations noted were due to the need for daily INR testing and dose adjustment. While most patients were initially admitted and started on therapy, the ease of administration of low molecular weight heparin during bridge therapy did not warrant admission and many patients chose to get discharged to prevent higher hospital bills. The pressure on the bed management systems in place also played a factor in discharging patients who were yet to achieve stable INR. Once discharged, several patients had difficulty in getting daily testing done due to rural homes or reduced mobility, while others withdrew to avoid the need altogether. Consequently there was a high attrition rate for that parameter.

Other limitations included the lack of outpatient INR testing availability on Sundays at our center. Consequently, if the principal investigator was unable to reach the patient in time to collect the blood test, this data was lost. Furthermore, since the randomization folder was kept under lock and key and only available for use during office hours, it was difficult to obtain access to the same after office hours for patients admitted from the emergency department. Other issues included dose administration after day 3, with different clinicians tending to have different opinions on dosing as compared to the dose nomogram, based on their assessment of the response to the drug noted.

Further limitations noted were the logistical difficulties of running a trial in a busy surgical division, with treating clinicians often unable to contact the investigators while they were occupied with routine duties such as surgery.

CONCLUSIONS

The most important conclusion of this trial was that the 10mg loading dose achieved adequate anticoagulation faster than the 5mg loading dose in our patient population. The question of safety was also addressed with no significantly higher rate of bleeding or over-anticoagulation. There was also no mortality. However, whether this translates to a shift in clinical practice guidelines is debatable as by day 5 both arms had similar levels of anticoagulation. It can however be said that patients may be effectively managed on an outpatient basis for this disease process with 10mg dose, as it would allow for shorter duration of expensive parenteral anticoagulation with low molecular weight heparin or fondaparinux.

Secondary objectives were mostly in keeping with international data on this disease process. However, we were also able to gather new data on the site of deep venous thrombosis in our patient population, noting that most patients admitted tended to have proximal deep venous thrombosis as compared to distal or calf vein thrombosis.

We do however note that there is a need for further study and analysis in this area before concrete clinical practice guidelines may be setup.

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ANNEXURES

PROTOCOLS

The basis of the trial protocols have been addressed in the materials and methods section. 60 recruited patients were randomized before initiation of warfarin therapy to the 10mg or 5mg arm. The patients were started on parenteral anticoagulation with unfractionated heparin, low molecular weight heparin or fondaparinux. Initiation doses were administered for two days according to the trial arm and the INR was tested on the morning of the third day. Subsequent dosing was decided by the treating clinicians based on the responses of the tested INR value. In keeping with standard practice, warfarin dose initiation was overlapped with injectable heparin, and INR testing was repeated daily until target INR was reached.

Clinicians were also allowed to decide to withdraw patients from trial if they felt that there was an increased risk of bleeding or if there was an unusual response to warfarin.

The dosage of warfarin from day 3 onwards was based on the clinician's decision. However, for the sake of reference the following schema was approved, regardless of the loading dosage.

Dosing Protocol:

INR Value	Day 3 dosage	Day 4 and beyond
<1.5	7mg	Add 2mg to previous dose
1.5-1.9	6mg	Add 1mg to previous dose
2.0-3.0	5mg	Continue same dose
3.1-3.5	4mg	Decrease 1mg from previous dose
3.5-4.0	3mg	Decrease 2mg from previous dose
>4.0	STOP	STOP – wait for two days and repeat INR

It was decided prior to the trial to define failure of warfarin induced anticoagulation as dosage with 15mg of warfarin for two days without achievement of therapeutic INR. However no patient had such a failure.

Additionally pre-designed nomograms were also studied for feasibility during pre-trial preparation. However these were felt to be unsuitable for use in our patients. (University of Utah health care thrombosis service nomograms from 1. Kovacs MJ, et al. Comparison of 10mg and 5mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. Annals of Internal Medicine 2003; 138: 714-719. 2. Crowther MA, et.al. Reply: Warfarin:less may be better. Annals of Internal Medicine 1997; 127 (4):333.)

PARTICIPANT INFORMATION AND CONSENT FORM

These were translated from English into Hindi, Tamil and Bengali.

Information Document

Description of the study

Acute deep vein thrombosis (DVT) is a disease where blood clots form in your veins and is treated by the administration of anticoagulants (‘blood thinners’) that help control clotting mechanisms in an individual. Anticoagulants are drugs that prevent harmful blood clots forming in your blood vessels by making your blood take longer to clot. The accepted standard of care for acute DVT involves initial administration of an injectable drug called heparin, overlapped with daily administration of an oral drug such as Warfarin that is continued for several weeks to months. The dosage of Warfarin is adjusted based on a blood test called INR, which indicates the body’s ability to clot blood. The Warfarin dose is considered adequate when the INR attained is stable between the values of 2 and 3, called the target INR.

Different initial doses of Warfarin can be given to achieve this target INR. The patient may be started on 5mg daily doses and then the dose adjusted based on the INR result. Another alternative is to start with 10mg daily doses and then adjust the dose to achieve the same INR. Through this study we wish to understand which dose achieves this INR value quickly, effectively and safely.

If you choose to take part in this study, basic information regarding your disease and medical history, and some information such as your age, gender, weight, mother tongue will be collected. You will then be randomly allotted to one of two groups by a computerized system. The first group will receive a 5mg Warfarin daily dose for two days and then the dose will be adjusted until the target INR is achieved. The second group will receive 10mg Warfarin daily dose for two days and then similarly the dose will be adjusted until the target INR is reached. The INR will be tested on the first day, the third day and then daily till the target INR is achieved. You will be discharged from the ward and the study when the INR remains in the target range for two consecutive days and can continue this treatment as an outpatient treated by your admitting unit.

From the third day onwards you will be required to fill out a form with a few questions aimed at determining whether or not you are developing a bleeding complication.

At any point should you develop excessive bleeding due to the drug or have a very high INR (greater than 8) adequate treatment shall be provided to correct the imbalance of clotting in your body. This may involve administration of drugs or the transfusion of blood products. Should you fail to respond to high doses of Warfarin, your treatment will be changed to another oral anticoagulant.

Further details about Warfarin, its uses and its side effects are provided below.

Information about Warfarin

Warfarin is the most common oral anticoagulant used today. It must be taken at the same time every day, washed down with a glass of water. Once the dose you need to take has been established, it is important that you take the same dose daily at the same time. Should you miss a dose, please take the same dose the next day at the same time without adding the missed dose.

Side effects: The most important side effect of this drug is bleeding. If you should develop any of the following please seek urgent medical attention –

• prolonged nosebleeds (more than 10 minutes);

• blood in vomit;

• blood in sputum;

• passing blood in your urine or faeces;

• passing black faeces;

• severe or spontaneous bruising;

• unusual headaches;

• for women, heavy or increased bleeding during your period or any other vaginal bleeding.

If you cut yourself, apply firm pressure to the site for at least five minutes using a clean, dry dressing.

Seek immediate medical attention if you:

• are involved in major trauma;

• suffer a significant blow to the head;

• are unable to stop bleeding.

Other side effects of Warfarin include alopecia (hair loss), allergic reactions, nausea, stomach or abdominal pain.

Please remember to tell any healthcare professional you take treatment from, or pharmacist you purchase over the counter drugs from about your ongoing treatment with Warfarin.

While on Warfarin treatment, please ensure the following –

- Take a balanced healthy diet. A sudden change in diet can change your body's clotting abilities and affect your INR.

- Strictly control consumption of alcohol. Restrict to three units a day for men, and up to two units a day for women. One pint of beer is two units; 25ml of a spirit is one unit; and 125ml of wine is one unit. Do not binge drink. Avoid consumption of alcohol altogether if possible.

- Please inform your doctor about any over the counter medications you are using. Many medications can interact with Warfarin and you made need a repeat INR tested 5 to 7 days after starting any new drug.

Other relevant information

As stated earlier, the standard treatment of acute deep vein thrombosis involves the use of oral anticoagulants. However, should you develop a complication directly related to the use of Warfarin, the study will bear the cost of your treatment. This will include the cost of medications required to correct your clotting capability and any additional tests required for the management of the complication or for its treatment.

The information we hope to gather from this process will be analyzed to help determine which dosage system is better suited to achieve the target INR for our patients quickly, safely and effectively. This information will help us guide therapy for other patients and plan further studies to better treat acute deep vein thrombosis.

Information you have provided for this study may be used in further studies carried out by this institution. Additionally you may be asked to take part in other studies and provide further information as part of follow up for analyses in other studies, and the decision to do so or not will be left entirely up to you.

We will ensure that the information you give us remains confidential and that your privacy is maintained.

You are free to access the data pertaining to your treatment on demand. We shall seek to publish the results of this study in a relevant medical journal..

You are free to refuse to participate in this study or to withdraw at any point in time. Your refusal or withdrawal will not affect the standard of care you would receive at our institution's health services.

The researchers for this study are doctors employed by the Christian Medical College, Vellore. The study is funded by the institutional review board of our institution.

The Institutional Review Board of Christian Medical College, Vellore has approved this study protocol.

Please feel free to ask us any doubts you may have regarding this study now or at any point during your stay at the hospital or treatment after study completion as an outpatient.

Consent Document

<u>Contact Names and Numbers</u>

If you have any questions about this study, you should talk to

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Conclusion

You will receive a signed copy of this form to keep.

I HAVE READ, OR HAD READ TO ME, THE ABOVE INFORMATION BEFORE SIGNING THIS FORM. I HAVE BEEN INFORMED THAT PARTICIPATION IN THIS IS VOLUNTARY, I HAVE BEEN OFFERED AN OPPORTUNITY TO ASK QUESTIONS AND HAVE RECEIVED ANSWERS THAT FULLY SATISFY THOSE QUESTIONS

PATIENT (SIGNATURE)	PATIENT NAME (PRINT)	DATE

PERSON OBTAINING (SIGNATURE)	PERSON OBTAINING NAME (PRINT)	DATE

Note to consent administrator: In the case of illiterate persons, the consent form will be read to him/her in the presence of a witness (not associated with the study) and a digital impression (thumbprint) will be obtained in place of a signature. The witness also needs to sign this form.

WITNESS (SIGNATURE)	WITNESS' NAME (PRINT)	DATE

CLINICAL RESEARCH FORM

1. Identification number:
2. Name of patient:
3. Hospital number:
4. Arm of trial (5mg or 10mg):
5. Age of patient:
6. Sex of patient:
7. Mechanism of deep venous thrombosis (provoked, unprovoked or recurrent):
8. Provoking factor (if provoked):
9. Side of disease (right, left or bilateral):
10. Site of disease (most proximal extent):
11. Duration of symptoms in days:
12. D-Dimer value:
13. Parenteral anticoagulant used (UFH/LMWH/Fondaparinux):
14. Baseline INR value:
15. Day 3 INR:
16. Day 4 INR:
17. Day 5 INR:
18. Day 6 INR:
19. Day 7 INR:
20. Day 8 INR:
21. Day 9 INR:

22. Day 10 INR:

23. Day 11 INR:

24. Day 12 INR:

25. Day 13 INR:

26. Day 14 INR:

27. Additional comment or note:

DATABASE

idno	arm	age	sex	mech	fact	side	site	dur	ddim
1	2	33	1	2		1	7	15	589
2	1	34	2	1	POSTPARTUM	2	7	4	9999
3	1	47	2	1	CA CERVIX	2	3	7	9999
4	2	55	1	2		1	3	30	953
5	1	55	1	3		2	3	30	659
6	2	60	1	1	TRAUMA	2	5	3	4179
7	2	63	1	1	TRAUMA	1	6	3	4179
8	2	20	2	1	TUBECTOMY	2	6	4	985
9	1	30	2	2		1	3	30	375
10	1	46	2	2		1	5	8	829
11	2	33	1	3		3	7	30	3823
12	1	50	1	2		2	5	4	2476
13	1	50	2	2		2	3	7	9999
14	2	45	1	2		2	6	14	3814
15	1	53	1	1	ICU STAY	1	4	8	9999
16	2	57	1	1	TRAUMA	1	1	30	1010
17	1	66	1	2		1	5	3	9999
18	2	24	1	2		1	6	5	1859
19	1	25	2	1	POSTPARTUM	1	5	2	1834
20	1	47	1	2		1	5	3	1942
21	2	52	1	2		1	4	3	2223
22	2	26	1	2		2	6	7	1159
23	1	63	2	1	CA ENDOMET	1	5	3	9999
24	2	68	1	3		2	5	20	741
25	1	49	2	2		3	7	20	998
26	2	35	2	2		1	3	3	715
27	2	47	1	1	SCLERO	1	2	1	206
28	1	36	2	3		1	4	7	773
29	2	42	1	3		3	4	15	212
30	2	46	2	3		3	4	20	9999
31	1	52	1	2		2	6	5	1188
32	1	66	1	1	CENTRAL LI	1	9	2	9999
33	2	58	1	3		3	99	15	993
34	1	44	2	3		2	5	2	2731
35	2	32	1	1	TRAUMA	1	5	10	1097
36	1	34	1	2		1	5	14	3329
37	1	36	2	2		2	6	20	9999
38	2	39	1	2		2	5	14	990
39	2	36	1	2		1	5	18	851
40	2	50	1	2		2	4	10	1024

41	1	61	1	1	TRAUMA	2	1	14	1102
42	1	32	2	2		3	4	30	9999
43	1	32	1	2		2	6	15	9999
44	2	51	2	1	OCP	2	5	6	1085
45	2	45	1	1	SURGERY	2	5	14	851
46	1	57	2	1	UNKNOWN CA	1	4	30	9999
47	1	33	1	2		2	6	15	996
48	2	50	2	2		2	6	1	4018
49	2	40	2	1	ADMISSION	2	5	2	999
50	2	26	1	2		1	5	5	3764
51	1	35	2	2		2	6	3	1152
52	1	77	2	1	TRAUMA	1	3	7	9999
53	1	43	1	1	ABDSURGERY	2	6	2	9999
54	2	58	2	1	TRAUMA	1	5	3	9999
55	2	45	2	1	OPPOIS/ICU	2	5	1	1137
56	2	53	2	3		2	4	7	933
57	1	67	1	3		2	99		1099
58	1	48	1	3		2	7	20	1178
59	1	24	2	1	POSTPARTUM	2	6	2	1153
60	2	65	1	2		2	5	7	4446

idno	inj	binr	n3inr	n4inr	n5inr	n6inr	n7inr	n8inr	n9inr	n10nr	n11nr	n12nr	n13nr	n14nr
1	2	0.99	99.99	99.99	99.99	3.26	3.74	3.71	2.46	1.75				
2	1	0.98	1.47	2.35	2.36									
3	1	1.23	99.99	3.1	6.9	9.8	2.8	1.11						
4	2	1.05	1.74	99.99	99.99	1.72	1.73	99.99	2.02	2.38				
5	3	1.1	1.68	3.76	7.61	8.49	6.54	99.99	4.24					
6	3	0.99	1.45	2.59	3.8	3.23	2.59	99.99						
7	3	1	1.66	2.25	2.89									
8	2	1.01	2.17	3.25	7.24	6.24								
9	2	1.24	2	99.99	99.99	99.99	7.1							
10	2	1.02	1.89	3.28	2.6	1.8	3.3	2.6	2.6					
11	1	1.81	3.01	3.11	99.99	99.99	2.62	99.99						
12	2	1.04	1.96	4.41	5.08	3.76	3.44	3.32	2.62	2.66				
13	2	0.97	0.97	1.03	1.06	1.18	1.51	1.82	2.58	99.99				
14	1	1.01	2.17	4.39	5.47	5.02	5.14	3.46	2.88	2.15				
15	1	1.07	4.74	7.98	99.99	99.99	99.99	2.74	99.99					
16	2	99.99	1.74	2	2.35									
17	3	1	1.1	1.29	1.79	2.28	99.99	99.99	1.29					
18	2	1.13	1.58	3.14	3.7	3.42	99.99	99.99	99.99	3.12	99.99			
19	2	1.06	1.13	1.49	2.04	2.23								
20	2	1.05	1.57	2.42	2.87									
21	2	99.99	1.74	2.58	2.17									
22	2	1	2.06	2.03										
23	2	99.99	1.41	2	3.65	3.88	2.69	1.88	99.99					
24	2	1.22	2.58	3.33	99.99	1.44	99.99							
25	2	0.97	1.06	1.26	1.27	1.69	2.22	2.44						
26	1	1.06	2.85	8.5	2.65	1.87	1.62	99.99						
27	1	1.11	3.8	3.51	3	99.99								
28	2	0.99	1.09	1.28	1.78	2.29	2.98							
29	1	99.99	1.94	3.5	3.1	99.99								
30	2	1.05	1.72	2.68	2.62									
31	3	1.06	1.41	2.07	3.33	3.55	99.9	2.95	99.9					

							9		9					
32	1	0.92	1.03	1.72	2.57	2.28								
33	2	1.17	1.9	1.29	1.49	1.7	99.99							
34	2	1.15	1.7	2.51	3.71	3.04	99.99	99.99	99.99	99.99	99.99	99.99	99.99	2.97
35	2	1.06	99.99											
36	2	0.98	1.22	1.9	3.8	3.8	2.63	99.99						
37	3	1.06	1.41	2.07	3.33	3.55	99.99	2.95	99.99					
38	2	1.65	6.67	8.43	99.99									
39	3	99.99	1.63	2.58	2.75									
40	2	0.99	1.21	1.6	2.09	2.6								
41	2	1.04	1.68	2.62	2.93									
42	3	0.93	2.22											
43	3	1.18	1.21	1.4	1.64	2.38	2.7							
44	3	99.99	2.5	2.8										
45	2	0.96	1.05	1.23	1.48	99.99	99.99	2.07	99.99	99.99	1.85			
46	3	99.99	3.86	10	10									
47	2	1.4	2.03	4.66	6.21									
48	2	0.98	1.44	2.2	99.99	2.5	99.99	99.99						
49	2	1.04	1.35	2.22	3.28	4.47	4.63	3.43	2.37	1.11	99.99	99.99	1.72	99.99
50	1	1.03	1.38	1.82	2.63	3.08	3.27	2.94	2.6					
51	2	9.3	1.79	2.97	99.99	99.99	4.23	99.99						
52	3	1.16	1.57	1.54	2.05	99.99	99.99							
53	2	0.9	0.9	1.42	2.61	3.87	99.99	99.99						
54	2	0.99	2.83	6.37										
55	2	1.04	2.69	5.1	5.18									
56	2	0.96	2.55	2.72										
57	9	1	1.18	1.73	99.99	99.99								
58	2	1.1	1.29	1.85	2.53	3.2	99.99	99.99						
59	2	0.96	1.5	2.27	3.5	99.99	99.99							
60	1	1.08	3.32	3.49	2.35	99.99	99.99							